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Squared frequency-*Kt/V*: a new index of hemodialysis adequacy—correlation with solute concentrations by computer simulation

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Abstract

Background: In patients undergoing home dialysis, conventionally, *Kt/V* has been regarded as an index of the removal efficiency per dialysis session. However, more recently, it has been considered that the hemodialysis product (HDP), rather than the *Kt/V*, is better associated with the clinical symptoms and outcomes in patients undergoing short daily dialysis or nocturnal dialysis. Nevertheless, the HDP lacks a theoretical background, and it does not take into consideration the dialyzer clearance or patient's body size. The aims of the present study were to clarify the theoretical validity of HDP focusing on its association with solute concentration by computer simulation and to propose a new index of hemodialysis adequacy.

Methods: We used compartment models and calculated the time course of urea and β_2 microglobulin (β_2MG) concentrations to determine the peak concentrations and time-averaged concentrations at varying dialysis frequencies ($n = 2$–7 sessions/week) and durations of dialysis per session ($t = 1$ to 8 h dialysis sessions).

Results: It was found that the peak concentrations of urea and β_2MG were significantly correlated with the HDP. Based on this, we theoretically extracted the factor related to the peak concentration and defined the squared frequency-*Kt/V* (*sf-Kt/V*), as a new index for determining hemodialysis adequacy ($sf\text{-}Kt/V = n^2Kt/V$; *K*, clearance; *V*, solute distribution volume; *n*, frequency; *t*, dialysis time); this index was well correlated with the peak concentrations of urea and β_2MG, even when the values of *K* and *V* were changed.

Conclusions: Since the *sf-Kt/V* is an index that reflects peak concentrations of urea and β_2MG, which takes into account the dialysis frequency, session duration, dialyzer clearance, and the body weight of the patient, it will be a very useful tool for determining appropriate dialysis schedules and dialysis conditions for individual patients.

Keywords: *Kt/V*, Hemodialysis product, Adequacy of dialysis, Home hemodialysis

Background

Home hemodialysis has the advantage that dialysis schedule (frequency and duration of dialysis) can be changed at the patients' own convenience. Many modalities of dialysis suitable for home hemodialysis have been proposed, including short daily dialysis [1], nocturnal dialysis [2–5], and daily nocturnal dialysis [6]. Home hemodialysis has been reported to be linked to increased survival [1, 7, 8], better blood pressure control [2], reduced left ventricular mass [4], improved mineral metabolism [4], enhanced quality of life [7, 8], and lower cost [2, 3, 5]. In home hemodialysis, since the dialysis schedule can be flexibly determined, a reliable index useful for determining the appropriate home dialysis modality, dialysis schedule (frequency and duration), and dialysis treatment conditions is required.

The *Kt/V* is a well-known index of the removal efficiency per dialysis session. To compare different dialysis modalities, the standard *Kt/V* was proposed as an index that can be uniformly used to measure and explicitly compare dialysis doses [9–11]. The use of this index was recommended by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines [12] in 2006 and also by the most recent KDOQI in 2015

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[13], to evaluate the optimal dialysis dose and schedule for frequent dialysis; however, it was still not widely used, probably because (1) its calculation process is quite complex; (2) the calculation required values of single-pool Kt/V and equilibrated Kt/V to fit the original definition of standard Kt/V, a mass generation per unit volume of body fluid normalized by the concentration; and (3) there is little advantage to use *standard* Kt/V as an alternative to Kt/V Daugirdas which has already been widely used in daily clinical practices for three times a week schedule.

It was also reported that the hemodialysis product (HDP), rather than the Kt/V, is better correlated with the clinical symptoms and outcomes in patients undergoing short daily dialysis and nocturnal dialysis, the modalities most often used for home hemodialysis [14]. HDP is an index of the adequacy of hemodialysis proposed by Scribner and Oreopoulos [14] in 2002 as their opinion. This index incorporates the dialysis frequency as an important variable:

$$\mathrm{HDP} = n^2 t$$

where n is the dialysis frequency [times/week], and t is the dialysis time per session [h/session].

HDP has been proposed simply based on the very positive results with more frequent dialysis reported by De Palma et al. [15], Buoncristiani et al. [16], Bonomini et al. [17], Pierratos et al. [2, 3], and Lockridge et al. [18]. The HDP has been shown to be well correlated with the patients' symptoms [14], and fewer symptoms [19–28] in dialysis patients has been reported in the treatment at HDP > 70, although these are retrospective observational studies where HDP has not been used as a treatment criterion. Use of the HDP as an index of the adequacy of hemodialysis has major limitations: it is an empirical index that lacks a physiological or theoretical background and ignores the effects of the dialyzer clearance and patient's body size. Therefore, although many types of dialyzers (low flux to super high flux) are currently available, it is difficult to select a dialyzer and operating condition suitable for short daily dialysis or nocturnal dialysis on the basis of the HDP.

The purpose of the present study was to explore a new index based on solute removal useful for ascertaining the adequacy of hemodialysis that would incorporate dialysis schedule (frequency and duration), the dialyzer clearance, and patient's body size. To this end, we first sought to identify factors (such as the time-averaged concentrations/peak concentrations) that are strongly correlated with the HDP using a kinetic model. From our results, we developed an index that was also well correlated with these factors and validated the index using a kinetic model.

Methods

Kinetic model for urea

We used the single-pool model (Fig. 1a) and calculated the time course of the concentrations of urea to determine the peak concentrations and time-averaged concentrations under various dialysis schedules (Table 1).

The change of the blood urea level during dialysis was calculated using the following equation:

$$\frac{V dC_{\mathrm{B}}(t)}{dt} = -K_{\mathrm{u}} C_{\mathrm{B}}(t) + G_{\mathrm{u}}$$

That is, $C_{\mathrm{B}}(t) = \frac{K_{\mathrm{u}} C_{\mathrm{B}}(0) - G_{\mathrm{u}}}{K_{\mathrm{u}}} e^{-\frac{K_{\mathrm{u}} t}{V}} + \frac{G_{\mathrm{u}}}{K_{\mathrm{u}}}$.

And the change of the blood urea level outside the period of dialysis was calculated by the following equation:

$$\frac{V dC_{\mathrm{B}}(t)}{dt} = -K_{\mathrm{u}} C_{\mathrm{B}}(t) + G_{\mathrm{u}}$$

That is, $C_{\mathrm{B}}(t) = \frac{G_{\mathrm{u}}}{V} t + C_{\mathrm{B}}(t_1)$

where C_{B} is the blood urea level, $C_{\mathrm{B}}(t_1)$ is the blood urea level at the end of dialysis, K_{u} is the urea clearance, and G_{u} is the endogenous production rate of urea. Using these equations, assuming $K_{\mathrm{u}} = 0$, and a steady state (we

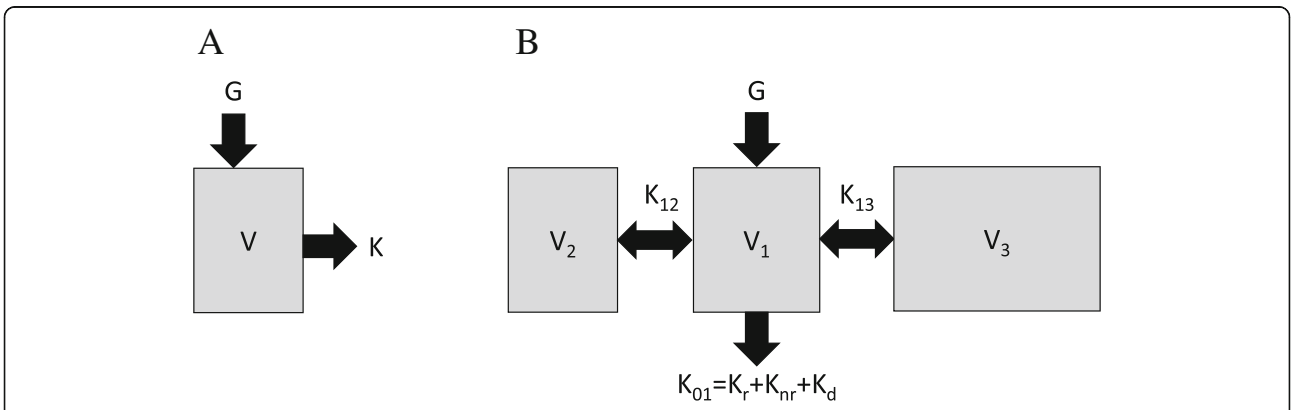

Fig. 1 Schematic diagram of single-pool (one-compartment) model (**a**) and three-compartment model (**b**)

Table 1 Setting conditions in the simulation

Group	A4	A5	A6	A7	A8	B4	B5	B6	B7	B8	C4	C5	C6	C7	C8	D3	D4
Dialysis frequencies [sessions/week]	2	2	2	2	2	3	3	3	3	3	4	4	4	4	4	5	5
Dialysis time per session [h/session]	4	5	6	7	8	4	5	6	7	8	4	5	6	7	8	3	4
HDP	16	20	24	28	32	36	45	54	63	72	64	80	96	112	128	75	100
Group	D5	D6	D7	D8	E2	E3	E4	E5	E6	E7	E8	F1	F2	F3	F4	F5	F6
Dialysis frequencies [sessions/week]	5	5	5	5	6	6	6	6	6	6	6	7	7	7	7	7	7
Dialysis time per session [h/session]	5	6	7	8	2	3	4	5	6	7	8	1	2	3	4	5	6
HDP	125	150	175	200	72	108	144	180	216	252	288	49	98	147	196	245	294

Time course of changes in the solute concentrations for various dialysis schedule was calculated (the dialysis frequency varied from 2 to 7 per week and/or dialysis time per session from 1 to 8 h)

repeatedly calculated the concentrations until the concentrations at the beginning and end of the week were equal), the time courses of the urea concentrations were calculated by the treatment conditions and the production rate of urea [29] (Table 2).

Kinetic model for β_2-microglobulin

Three-compartment models (Fig. 1b) in which β_2-microglobulin (β_2MG) was distributed in a slowly moving pool and fast moving pool were used to calculate the time courses of β_2MG concentration under various dialysis schedules (Table 1). The values of total clearance, intercompartmental clearance parameters, and compartmental volumes reported by Odell et al [30] for β_2MG were used. The equation of mass transfer in each compartment could be expressed by the following equations:

$$\frac{V_1 dC_1}{dt} = -(K_{01} + K_{12} + K_{13})C_1 + K_{12}C_2 + K_{13}C_3 + G_\beta$$

$$\frac{V_2 dC_2}{dt} = K_{12}C_1 - K_{12}C_2$$

$$\frac{V_3 dC_3}{dt} = K_{13}C_1 - K_{13}C_3$$

$$K_{01} = K_r + K_{nr} + K_d$$

$$V_d = V_1 + V_2 + V_3$$

where K_r, K_{nr}, and K_d are the renal, non-renal, and dialyzer clearance, respectively. The distribution volume, V_d, is the sum of the compartmental volumes, and G_β is the endogenous production rate of β_2MG. The differential equations were solved numerically using a Runge-Kutta routine, using reported values [30] (Table 3). The time courses of the solute concentrations were calculated by the treatment conditions, such as the mass transfer coefficient between pools, solute production, and clearance of dialyzer.

We compared the correlation between the peak concentrations/time-averaged concentrations of solutes and the HDP, total dialysis time, or squared frequency-*Kt*/*V* (*sf-Kt*/*V*), by determining the coefficients of determination (R^2), likelihood (L), and Akaike Information Criterion (AIC).

Model fitness

Regarding HDP (n^2t) and total dialysis time (nt), we compared which one better estimates peak concentration and time-averaged concentration. Wilcoxon's signed-rank sum test was used to check whether there was a significant difference in the absolute value of the difference between the approximate curves calculated by a least squares method and the calculated values by simulation.

Likelihood ratio test was used to compare the HDP (n^2t, degree of freedom is 2) and *sf-Kt*/*V* (degree of freedom is 4). We compared the fitness between the HDP or the *sf-Kt*/*V* and the peak concentrations of small molecules at varying dialyzer clearances (Fig. 4a, b), and the fitness between the HDP or the *sf-Kt*/*V* and the

Table 2 Treatment conditions used to calculate the time courses of urea concentration using a single-pool model

Clearance of urea, K_u	90, 120, 150, 180	[mL/min]
Endogenous production rate of urea, G_u	6.2	[mg/min]
Fluid volume before the start of dialysis, V	36,000	[mL]

Table 3 Treatment conditions used to calculate the time courses of β_2MG concentration using a three-compartment model

Clearance of β_2MG, K_β	40, 60, 80	[mL/min]
Non-renal clearance, K_{nr}	2.82	[mL/min]
Renal clearance, K_r	0	[mL/min]
Intercompartmental clearance, K_{12}	75	[mL/min]
Intercompartmental clearance, K_{13}	28.8	[mL/min]
Endogenous production rate, G_β	0.159	[mg/min]
Fluid volume before the start of dialysis, V	36,000	[mL]
Volume of compartment 1 per body weight	53	[mL/kg]
Volume of compartment 2 per body weight	39	[mL/kg]
Volume of compartment 3 per body weight	109	[mL/kg]

time-averaged concentrations of urea and β_2MG at varying dialyzer clearances (Fig. 4c, d).

First, the maximum log likelihood (L) was calculated from the residual sum of squares of the approximate curves and the calculated values by simulation by the following equation.

$$\log L = -\frac{N}{2}\left(\log(2\pi) + \log\sigma^2 + 1\right)$$

where σ^2 is the maximum likelihood estimator of variance, and N is sample size. The difference of the deviance was calculated by multiplying log L by − 2,

$$\Delta D = -2\log L_{\mathrm{HDP}} - (-2\log L_{\mathrm{sf-Kt/V}})$$

We performed a chi-square test for ΔD with a difference of 2 degrees of freedom to compare HDP with *sf-Kt/V* regarding which one would be better for fitting to the peak concentrations of urea and β_2MG at varying dialyzer clearances.

AIC was also calculated by the following equation:

$$\mathrm{AIC} = -2L + 2 \times (\text{number of parameters})$$

When the AIC is smaller, the model is considered to be a better fitting model after taking into account the number of parameters used.

Results

Search for factors correlated with the HDP

We assumed that if we could identify the factors that were more strongly correlated with the HDP than with the total weekly dialysis time, we would be able to estimate why HDP (n^2t) is better correlated with the clinical symptoms than the total weekly dialysis time (nt). We focused on the peak concentrations and time-averaged concentrations of solute molecules per week. We used a single-pool model to investigate the kinetics of urea and a three-compartment model to investigate the kinetics of β_2MG [30].

The time courses of solute concentrations under various dialysis schedules (varying dialysis frequencies from 2 to 7/ week and varying dialysis times per session from 1 to 8 h/session) were calculated (Table 1). We determined the peak concentrations and time-averaged concentrations for each solute.

The peak concentrations of all molecules were found to be significantly better correlated with the HDP than with the weekly total dialysis time (Fig. 2). While the time-averaged concentrations of urea were more tightly correlated with weekly total dialysis time than with HDP (Fig. 3). Thus, our results suggested that the HDP is strongly correlated with the peak concentrations of urea and β_2MG.

The "unphysiological nature" of dialysis may also be demonstrated by the difference between the maximum and minimum concentrations. This parameter was, however, not well correlated with HDP (data not shown).

We propose HDP × K/V ($n^2t \times K/V$) as a new index called *sf-Kt/V* (Appendix). This index incorporates both solute removal (K) and fluid volume of the patient (V), whereas the HDP does not. We then investigated whether this index would still be well correlated with the peak concentrations of small molecules when the clearance of the dialyzer was varied. The correlation of the *sf-Kt/V* with the concentrations showed higher R^2 and lower AIC than that of HDP, and the difference in maximum log likelihood (deviance) was statistically large, meaning that the *sf-Kt/V* showed significantly better correlations with the peak concentrations of small molecules than HDP (Fig. 4). In other words, while the correlations with the HDP became weak when we used a different dialysis clearance, the *sf-Kt/V* still showed strong correlations with the peak concentrations of urea. Since *sf-Kt/V* is obtained by multiplying HDP by K/V, that is, the dialyzer clearance and patient's body weight is also considered in the calculation of the *sf-Kt/V*; this index is deemed as being a useful new index for comparing the adequacy of dialysis based on solute removal (dialysis dose).

While no precise threshold value of the HDP has been determined based on clinical evidence, HDP > 70 proposed by Scribner and Oreopoulos [14] is well accepted as being indicative of adequate dialysis. In a patient with a dry weight of 60 kg (body fluid volume, 36 L) undergoing dialysis with a dialyzer providing an average urea clearance of 160 mL/min and HDP > 70 will be equivalent to *sf-Kt/V* > 18.7.

Assuming that HDP > 70 is the threshold value for determining the adequacy of dialysis, we would determine the treatment schedules at varying dialyzer clearances (Fig. 5) and varying patient body weights (Fig. 6) that would yield *sf-Kt/V* values of over 20. When conducting dialysis four times a week, 6-h dialysis sessions are enough to obtain an HDP value of over 70 ($4^2 \times 6 = 96$; > 70), regardless of the dialyzer urea clearance. When *sf-Kt/V* is used, and if patient weight was 60 kg, it can be judged that sufficient solute removal would be obtained when the dialyzer clearance is 180 mL/min or 150 mL/min, but equivalent solute removal cannot be obtained with 6-h sessions when the dialyzer urea clearance is 120 mL/min or 90 mL/min (Fig. 5), which would occur when blood flow rate or dialysate flow rate set to lower value. The appropriate dialysis frequency and dialysis time per session would also be calculated depending on the patient's body weight (Fig. 6).

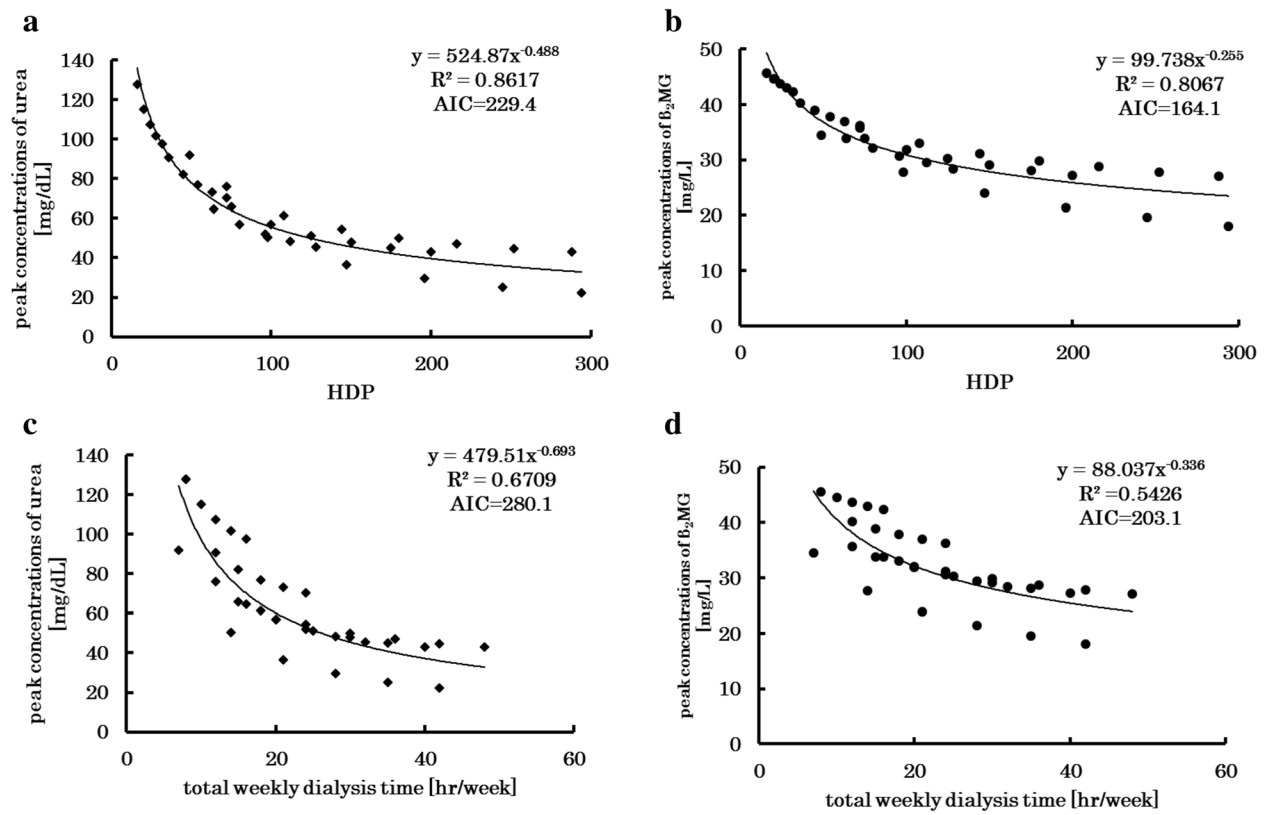

Fig. 2 Peak concentrations vs. HDP and total weekly dialysis time. Relationships between the HDP and peak concentrations of small molecules (**a**) and β_2MG (**b**) for various dialysis schedules and the relationships between the total weekly dialysis time and peak concentrations of urea (**c**) and β_2MG (**d**). The peak concentrations were significantly better correlated with the HDP than the total weekly dialysis time ($p = 0.0034$ for urea, $p = 0.0171$ for β_2MG)

Discussion

The results of simulations revealed strong correlations of the HDP with the peak concentrations of urea and β_2MG. Considering these results and the fact that the HDP was empirically related to the clinical symptoms of patients, from viewpoint of solute removal, a large value of HDP would mean smaller peak concentrations, which could explain the reduction of the clinical symptoms.

In the field of pharmacokinetics, the toxicity of the substances is known to be time-dependent and concentration-dependent [31]. The experience that greater the HDP led to lighter the symptoms in dialysis patients [14] and the results we obtained that peak concentration of urea and β_2MG better correlated with HDP than total dialysis time suggest that the toxicity due to accumulated substances in dialysis patients may concentration-dependent.

Since the results obtained here may be dependent on the parameters listed in Table 3, we have illustrated how the results would change when other values are selected for the relevant parameters. When the parameter changed by about 20%, which was the standard deviation of the measured data in the patients [30] (Table 4), the percent changes of the peak (Table 5) and time-averaged concentrations (Table 6) were determined. Intercompartmental clearances and volumes of the compartments changed the concentration by a few percentage points, and the endogenous production rate of β_2MG changed the concentration by 25%. However, the difference among the schedules was only a few percentage points, which would be expected to have had no significant influence on the correlation between the HDP and the peak concentration or time-averaged concentration.

Ultrafiltration and intercompartmental fluid shift may somehow have an influence, especially the concentrations of intermediate-sized molecules like β_2MG. We checked the effects of ultrafiltration (data not shown). The results were similar to those obtained without taking into consideration ultrafiltration, for both urea and β_2MG. In regard to intercompartmental fluid shift, we can discuss the results of the effects of the changes in the volumes of the compartments and intercompartmental clearances. The differences in the peak and time-averaged concentrations among the schedules obtained by varying the values of these parameters were

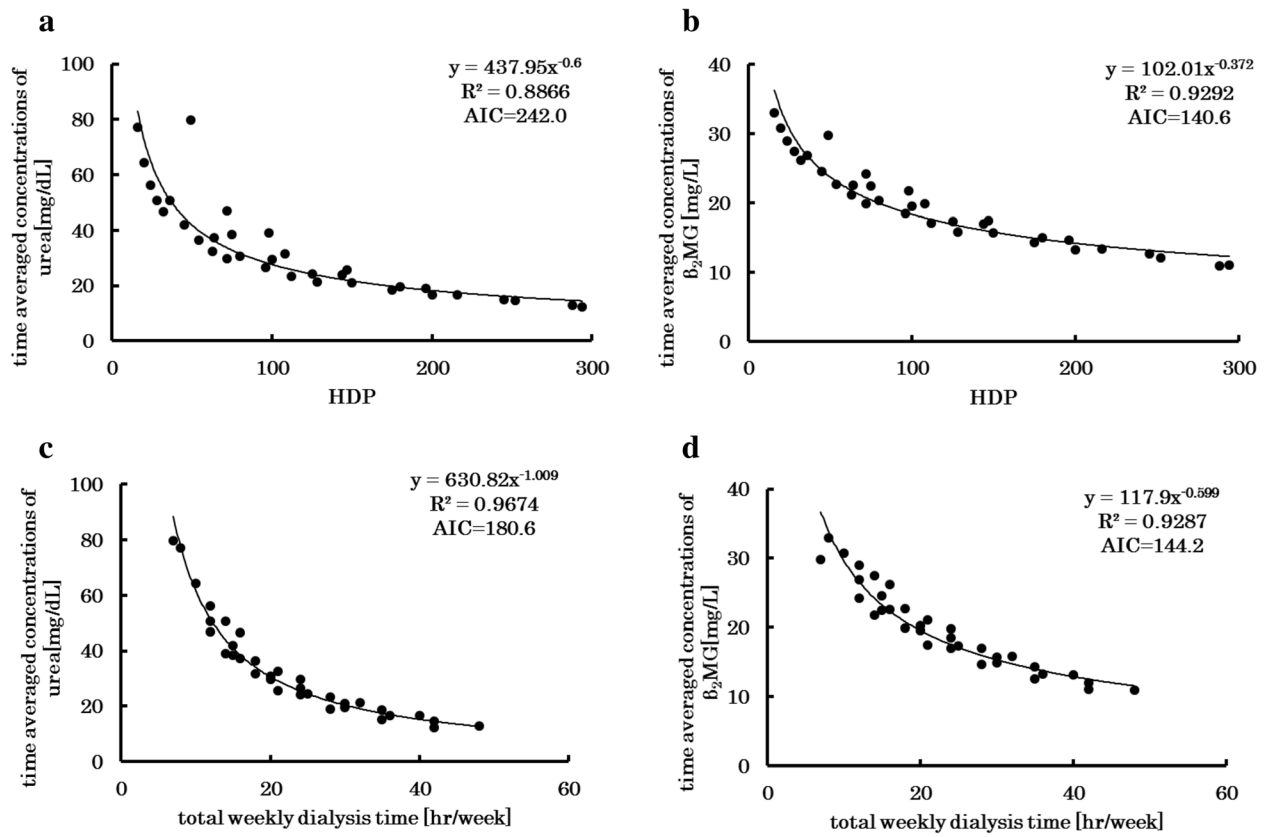

Fig. 3 Time-averaged concentrations vs. HDP and total weekly dialysis time. Relationships between HDP and the time-averaged concentrations of urea (**a**) and β_2MG (**b**) for various dialysis schedules and relationships between the total weekly dialysis time and the time-averaged concentrations of urea (**c**) and β_2MG (**d**). The time-averaged concentrations of small molecules were significantly better correlated with the total weekly dialysis time than the HDP ($p = 0.0004$ for urea, $p = 0.6261$ for β_2MG)

only a few percentage points, which would be expected to have exerted no significant influence on the correlations between the HDP and peak concentration or time-averaged concentration.

The average weekly clearance per week, that is, EKR, is expressed using time-averaged concentration (TAC) and generation rate as [32, 33]:

$$\mathrm{EKR} = (G/\mathrm{TAC}).$$

If dialysis is performed n times per week with the same clearance, same dialysis time, and same intervals between the dialysis treatments, the concentration changes during the n dialysis sessions per week would be equal and the total removal amount per week can be calculated as:

$$\mathrm{EKR}T_\mathrm{w} = nKt,$$

where T_w is the total number of minutes in the week = 168 h. In actual clinical situations, although the intervals between dialysis treatments are not the same and the TAC is estimated from limited sampled data (the exponential decrease in the concentration was not taken into consideration), we may approximate the above as:

$$\mathrm{EKR}T_\mathrm{w} \fallingdotseq nKt.$$

This approximation has been shown as a good approximation for thrice-weekly therapy [34]. Therefore, using this approximation:

$$\mathrm{TAC} = GT_\mathrm{w}/nKt = (1/nt)(GT_\mathrm{w}/K).$$

This approximation can lead to a difference from the actual value. The difference is considered to be attributable to the intervals between dialysis treatments being different (therefore, the concentrations at the beginning of each dialysis session are not the same), and the fact that G, K, and V cannot be regarded as constant [34].

This equation shows that the time-averaged concentration of urea is inversely proportional to the total dialysis time per week (nt). It is obvious from the theoretical point of view that the time-averaged concentration would be well correlated with the total dialysis time. In the simulation of the present study, we obtained TAC = 630 $t^{-1.0}$ in

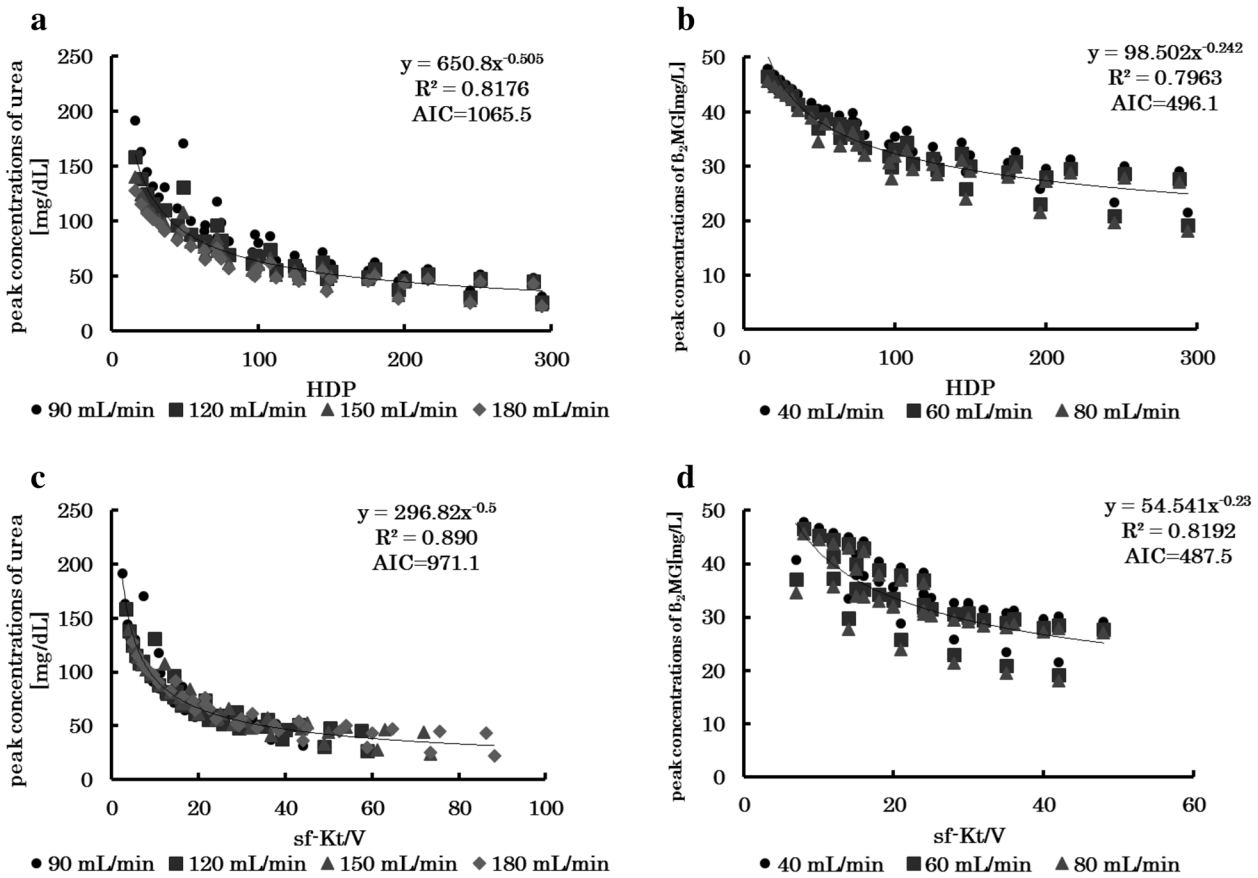

Fig. 4 Peak concentrations vs. HDP and *sf-Kt/V*. Relationships between the HDP (**a**) or the *sf-Kt/V* (**c**) and the peak concentrations of urea at for varying dialyzer clearances and relationships between the HDP (**b**) or the *sf-Kt/V* (**d**) and the peak concentrations of β_2MG at varying dialyzer clearances. When we entered different dialysis clearances, the *sf-Kt/V* showed significantly better correlations with the peak concentrations of both urea and β_2MG than HDP ($p < 0.01$ for both cases)

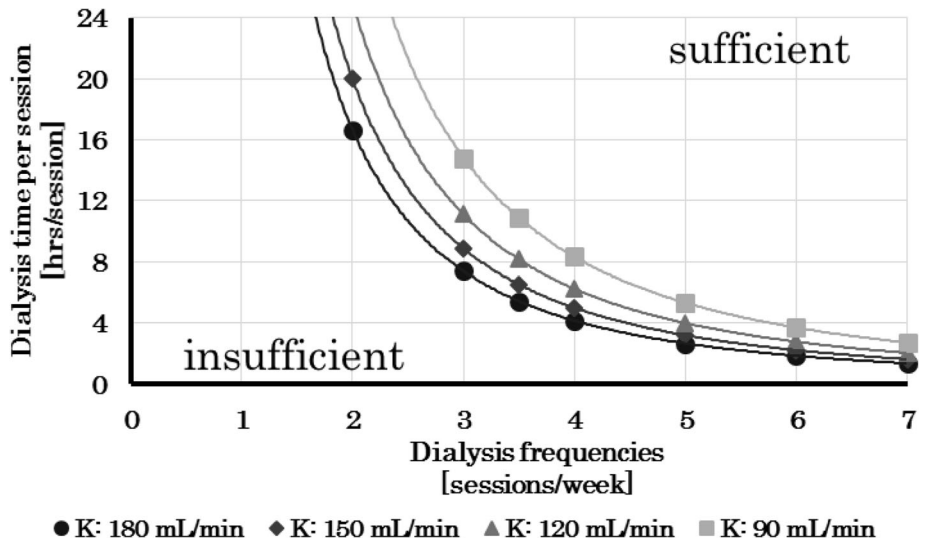

Fig. 5 Dialysis schedules that would yield *sf-Kt/V* values of over 20 for varying dialyzer clearances at constant *V* ($V = 36{,}000$ mL). Each line shows the schedule that would yield an *sf-Kt/V* of 20. The area above this line represents the dialysis times/frequencies that yield *sf-Kt/V* values of over 20. As the dialyzer clearance increases, the dialysis time/frequency needed to obtain an *sf-Kt/V* value of over 20 decreases

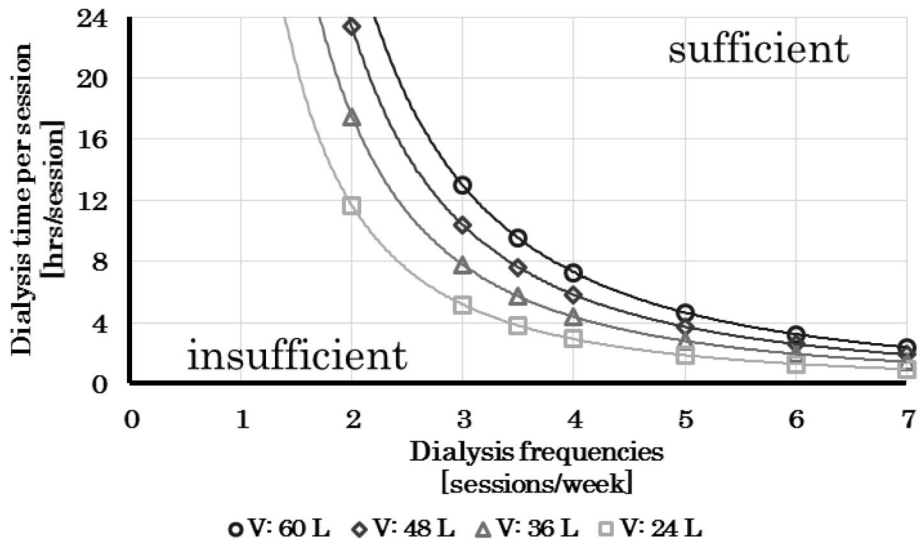

Fig. 6 Dialysis schedules that would yield *sf-Kt/V* values of over 20 for varying body weights of the patient at constant *K* (*K* = 180 mL/min). Each line shows the schedule that would yield an *sf-Kt/V* value of 20. The area above this line represents the dialysis times/frequencies that yield *sf-Kt/V* values of over 20. As the body weight of the patient increases, the dialysis time/frequency needed to obtain an *sf-Kt/V* value of over 20 increases. Thus, the optimal dialysis schedule depends on the patient's body weight

Fig. 2d, implying that the dataset (dialysis frequency and dialysis time for each session) was selected with little bias and the influence of time and frequency of dialysis on the peak concentration and average concentration can be adequately investigated using this dataset.

Therefore, in this study, a new index *sf-Kt/V* was devised considering the factors influencing the peak concentrations, $sf\text{-}Kt/V = n^2Kt/V$. The *sf-Kt/V* was established as an indicator showing strong correlations with the peak concentrations. Since *sf-Kt/V* is an indicator based on solute removal that takes the dialyzer clearance and patient's body size into consideration, it can be used to propose a dialysis schedule appropriate for each individual patient and to determine the appropriate dialyzer clearance, dialysis time, dialysis frequency, etc.

Scribner and Oreopoulos recommended HDP > 70 based on the 30-year excellent survival outcome in Tassin [19–23]. HDP > 70 is equivalent to *sf-Kt/V* > 20 when the dialyzer used assumed to have an average urea clearance is 160 mL/min and the average dry weight of the patient is 60 kg. Therefore, assuming that HDP > 70 is a threshold value for determining the adequacy of dialysis, it can be considered that an *sf-Kt/V* value of about 20 for urea may be an approximate threshold of an indicator of the adequacy of dialysis. Currently, there are no data on comparisons of the clinical efficacy using *sf-Kt/V* as an indicator, and we propose to analyze clinical data in the future to establish a satisfactory threshold of *sf-Kt/V*. As this threshold value can be determined for each solute, it is necessary to clarify these thresholds not only for urea but also for β_2MG.

When we calculate *sf-Kt/V*, single-pool *Kt/V* can be used for urea and equilibrated *Kt/V* for β_2MG as *Kt/V*. For simple calculation to determine the dialysis schedule, dialysis time, and dialyzer clearance, we can use *K* as the dialyzer clearance corrected by the blood and dialysate flow rate, *t* as the dialysis time, and *V* as the estimated body fluid volume. However, if we use this simple calculation, *sf-Kt/V* would be affected by the differences between the estimated and actual body fluid volume and between the calculated clearance and actual clearance caused by a decrease in the actual blood flow rate or recirculation. Therefore, when conducting cohort studies or randomized controlled trials to determine the threshold value of *sf-Kt/V*, it is considered better to use single-pool *Kt/V* for urea and equilibrated *Kt/V* for β_2MG for the calculation of *sf-Kt/V*.

There were several limitations of the present study. This study was not a clinical study. Whether it is indeed an appropriate index is yet to be confirmed by a cohort study

Table 4 Values of the parameters of three-compartment model applied for measured data of β_2MG in patients [30]

	V_1 [mL/kg]	K_{nr} [mL/min/kg]	V_2 [mL/kg]	K_{12} [mL/min/kg]	V_3 [mL/kg]	K_{13} [mL/min/kg]	G_β [mg/hour/kg]
Mean ± SD	53 ± 9	0.047 ± 0.010	39 ± 11	1.25 ± 0.25	109 ± 27	0.48 ± 0.09	0.159 ± 0.041
Ratio of SD [%]	± 17	± 21	± 28	± 20	± 25	± 19	± 26

Data were expressed per kg body weight

Table 5 The percent changes of the peak concentrations determined by the calculation using maximum and minimum value (mean ± SD) of each parameter shown in Table 3

	Dialysis schedule		Percent changes of peak concentrations [%]						
	n	*t*	V_1	K_{nr}	V_2	K_{12}	V_3	K_{13}	G_β
Maximum value (mean + SD)	2	7	− 1.76	− 11.30	− 2.07	− 0.02	− 3.28	− 0.56	25.79
	3	4	− 1.69	− 10.61	− 2.09	− 0.06	− 2.80	− 0.69	25.77
	5	7	− 2.45	− 6.76	− 3.18	− 0.04	− 4.58	− 1.02	25.89
	7	4	− 3.02	− 5.63	− 2.99	− 0.19	− 1.34	− 1.97	25.78
Minimum value (Mean − SD)	2	7	1.81	13.93	2.18	0.03	4.12	0.74	− 25.79
	3	4	2.04	13.08	2.32	0.09	3.72	0.83	− 25.65
	5	7	2.98	7.67	3.66	0.06	6.27	1.45	− 25.77
	7	4	3.49	6.35	3.63	0.29	2.47	2.49	− 25.79

or randomized controlled trial. Furthermore, *sf-Kt/V* > 20 was also calculated by assuming that HDP > 70 is the threshold value for determining the adequacy of the dialysis schedule; however, HDP > 70 has not yet been confirmed by clinical trials whether this threshold value is appropriate or not. When K = 180 mL/min, V = 36,000 mL, the dialysis duration that would yield *sf-Kt/V* values of over 20 was calculated as 8 h, meaning Kt/V = 2.4. Current dialysis guidelines for hemodialysis prescription [35] recommend Kt/V = 1.4 or more as the target dose for thrice-weekly dialysis. How to ensure consistency with the current guideline is an important issue while using this index. *sf-Kt/V* is also not a precise index, like the standard Kt/V or EKR, and does not reflect the residual kidney function. However, it does reflect the peak concentrations of the accumulated solutes in dialysis patients. With further clinical studies, this index has the potential to become a better indicator for determining the adequacy of dialysis in individual patients.

Conclusions

The *sf-Kt/V* is an index that takes into account the dialysis frequency, session duration and clearance, and the body weight of the patient and correlates with the peak concentrations more tightly than HDP. It offers the promise of being a very useful index for determining appropriate dialysis schedules and dialysis conditions for individual patients.

Appendix

Development of a new index and its validation

Taking into account the results that the peak concentrations of small molecules were better correlated with the HDP than with the total dialysis time and that the HDP has been shown to be well correlated with the clinical symptoms [14], we considered the peak concentrations of small molecules as the candidate factors closely related to the clinical symptoms.

Using a simple kinetic model ignoring changes of the body weight associated with water removal and intake, the concentrations of the solutes just before dialysis for thrice-a-week dialysis were calculated using the following equations:

$$C_1 = C_0 \ \exp\left(-Kt/V\right) + GT_1/V$$

$$C_2 = C_1 \ \exp\left(-Kt/V\right) + GT_2/V$$

Table 6 The percent changes of time-averaged concentrations determined by the calculation using maximum and minimum value (mean ± SD) of each parameter shown in Table 3

	Dialysis schedule		Percent changes of time-averaged concentration [%]						
	n	*t*	V_1	K_{nr}	V_2	K_{12}	V_3	K_{13}	G_β
Maximum value (mean + SD)	2	7	− 2.10	− 8.94	− 2.27	− 0.07	− 0.40	− 1.88	25.79
	3	4	− 1.88	− 8.92	− 1.89	− 0.18	0.65	− 1.75	25.75
	5	7	− 2.40	− 4.98	− 2.79	− 0.12	− 0.33	− 2.30	25.82
	7	4	− 2.79	− 5.08	− 2.30	− 0.33	1.29	− 2.23	25.74
Minimum value (mean − SD)	2	7	2.25	10.75	2.57	0.11	1.15	2.45	− 25.79
	3	4	2.36	10.85	2.40	0.30	− 0.56	1.96	− 25.76
	5	7	2.99	5.56	3.33	0.19	1.13	3.05	− 25.77
	7	4	3.09	5.66	3.00	0.46	− 1.48	2.52	− 25.82

$$C_0 = C_2 \ \exp\left(-Kt/V\right) + GT_3/V$$

where K is the dialysis clearance [mL/min]; t is the dialysis time per session [min]; T_1, T_2, and T_3 are the inter-dialysis times; V is the body fluid volume [mL]; and G is the generation of solutes [mg/min].

If T_3 is the maximum dialysis interval, C_0 becomes the peak concentration per week, C_{peak}:

$$C_{\mathrm{peak}} = \frac{\frac{G}{V}\left\{T_3 + T_2 \ \exp{-}\left(\frac{-Kt}{V}\right) + T_1 \ \exp\left(\frac{-2Kt}{V}\right)\right\}}{1 - \ \exp\left(\frac{-3Kt}{V}\right)}$$

Similarly, in the case of four-times-a-week dialysis, the following equation can be obtained.

$$C_{\mathrm{peak}} = \frac{\frac{G}{V}\left\{T_4 + T_3 \ \exp{-}\left(\frac{-Kt}{V}\right) + T_2 \ exp\left(\frac{-2Kt}{V}\right) + T_1 \ \exp{-}\left(\frac{-3Kt}{V}\right)\right\}}{1 - \ \exp\left(\frac{-4Kt}{V}\right)}$$

From these equations, in the case of the condition that the Kt/V is greater than 1, the peak concentration, C_{peak}, will become higher when the maximum dialysis interval becomes longer, or when the dialysis frequency (n) decreases or the Kt/V becomes less.

Therefore, the peak concentration would be well correlated with:

$$n\left(\frac{Kt}{V}\right)\left(\frac{1}{T_{\max}}\right),$$

where $T_{\max}$ is the maximum interval between dialysis sessions [h].

This can be arranged into a dimensionless form as $n(\frac{Kt}{V})(\frac{T_{\mathrm{w}}}{T_{\max}})$

This index should be well correlated with the C_{peak}. If the intervals between dialysis sessions are equal, then:

$$T_{\max} \fallingdotseq \frac{T_{\mathrm{w}}}{n},$$

and the following equation can be obtained.

$$n\left(\frac{Kt}{V}\right)\left(\frac{T_{\mathrm{w}}}{T_{\max}}\right) \fallingdotseq n^2\left(\frac{Kt}{V}\right) = n^2 t\left(\frac{K}{V}\right)$$

Because HDP = n^2t, it is easy to conceive why the peak concentrations of small molecule solutes are well correlated with the HDP as well as this index. This index incorporates both solute removal (K) and fluid volume of the patient (V), whereas the HDP does not. Therefore, this index can be used more flexibly, and we propose this index as a new index called squared frequency-Kt/V (*sf-Kt/V*).

Abbreviations

AIC: Akaike Information Criterion; C_B: Blood level [mg/mL]; C_{peak}: Peak concentration per week [mg/mL]; EKR: Average weekly clearance per week [mL/min]; G_u: Endogenous production rate of urea [mg/min]; G_β: Endogenous production rate of β_2-microglobulin [mg/min]; HDP: Hemodialysis product; K: Dialysis clearance [mL/min]; K_d: Dialyzer clearance [mL/min]; K_{nr}: Non-renal clearance [mL/min]; K_r: Renal clearance [mL/min]; K_u: Clearance of urea [mL/min]; L: Likelihood; n: Dialysis frequency [sessions/week]; N: Sample size; R^2: Coefficients of determination; *sf-Kt/V*: Squared frequency-*Kt/V*; t: Dialysis time per session for HDP [h/session]; t: Dialysis time per session [min/session]; T_1, T_2, T_3: Inter-dialysis times [min]; TAC: Time-averaged concentration [mg/mL]; T_w: Total number of minutes in a week (10,080 min) [min]; V: Body fluid volume [mL]; V_1, V_2, V_3: Volume of compartments 1, 2, and 3 per body weight [mL/kg]; V_d: The sum of the compartmental volumes [mL]; β_2MG: β_2-microglobulin; σ^2: Maximum likelihood estimator of variance

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