TIME-AVERAGED HIGH-SENSITIVITY C-REACTIVE PROTEIN PREDICTS MORTALITY AND DROPOUT IN PERITONEAL DIALYSIS PATIENTS

Ya-Chung Tian, Shou-Hsuan Liu, Yi-Jung Li, Hsin-Hsu Wu, Cheng-Chia Lee, Kun-Hua Tu, Chan-Yu Lin, Yung-Chang Chen, Ming-Yang Chang, Yu-Ming Chen, Hsiang-Hao Hsu, Chih-Wei Yang

Kidney Research Center, Department of Nephrology, Lin-Kou Chang Gung Memorial Hospital and Department of Medicine, Chang Gung University, Taoyuan, Taiwan

Background

We previously demonstrated the importance of obtaining a single baseline serum HS-CRP measurement for predicting the 2-year mortality and dropout including death or transfer to hemodialysis (HD) in peritoneal dialysis (PD) patients independent of age, diabetes, hypoalbuminemia, and the occurrence of cardiovascular events. However, serum CRP levels vary and are increased for only a fraction of time in any given dialysis patient. The aim of this observational cohort study was to explore whether the time-averaged serum HS-CRP level is superior to a single baseline measurement for predicting 5-year mortality and dropout in PD.

Patients and methods

Totally 335 patients receiving PD for more than 3 months and regular HS-CRP examination at 12-month intervals were recruited in this study. All patients were followed up for 60 months and the clinical parameters and outcomes were recorded regularly. The patients were stratified into 3 tertiles according to their time-averaged serum HS-CRP levels. Patients were excluded if they had acute events (active infection, acute cardiovascular or cerebrovascular disease) occurring within 1 month before and after each HS-CRP measurement, less than two separate measurements of HS-CRP during the entire follow-up period, the diagnosis of malignancy or encapsulating peritoneal sclerosis (EPS) before January 2010, or loss to follow-up.

Baseline demographic and clinical data, such as sex, age, body mass index (BMI), the presence of comorbidities such as diabetes mellitus (DM), coronary artery disease (CAD), congestive heart failure (CHF), stroke, systemic lupus erythematosus (SLE), liver cirrhosis, hepatitis B, and hepatitis C, the duration of PD at study entry, the PD modality (automated PD or continuous ambulatory PD), the use of icodextrin, the dialysate calcium level (2.5mEq/L or 3.5mEq/L), residual urine, hemogram, and biochemical parameters were obtained. PD membrane characteristics such as dialysate-to-plasma concentrations for creatinine (D/P$_{Cr}$), results of the peritoneal equilibrium test (PET), total weekly Kt/V urea, and total weekly creatinine clearance (CCr) were assessed. During the 60-month follow-up, clinical outcomes such as cardiovascular event(s), infection episode(s), newly developed malignancy, encapsulating peritoneal sclerosis (EPS), dropout (death plus conversion to hemodialysis), and mortality were recorded. Residual urine was defined as a daily total urine volume of more than 100 mL. Cardiovascular events were defined as at least once acute myocardial infarction or cerebral vascular accident during the entire follow-up period. Infection episodes were defined as at least once PD-related or non-PD-related infection during the entire follow-up period.

Results

Table 1 Baseline demographic and laboratory characteristics of the PD patients categorized according to time-averaged serum HS-CRP levels

Time-averaged serum HS-CRP (mg/L)	Total (n = 335) 9.18 ± 12.28 (0.25 ~ 109.47)	Lower tertile (n= 112) 1.38 ± 0.67 (0.25 ~ 2.65)	Middle tertile (n = 111) 5.07 ± 1.69 (2.66~ 8.55)	Upper tertile (n = 112) 21.05 ± 15.16 (8.58 ~ 109.47)	P-value
Male	115 (34.3)	37 (33.0)	41 (36.9)	37 (33.0)	0.778
Age (years)	48.7 ± 13.5	46.4 ± 13.7	47.0 ± 12.6	52.6 ± 13.5	0.001
Body mass index (Kg/m²)	22.5 ± 3.6	21.5 ± 3.1	22.6 ± 3.2	23.4 ± 4.1	<0.001
DM	54 (16.1)	10 (8.9)	14 (12.6)	30 (26.8)	0.001
CAD	10 (3.0)	1 (0.9)	2(1.8)	7 (6.3)	0.042
CHF	21 (6.3)	7 (6.3)	9(8.1)	5 (4.5)	0.533
Stroke	18 (5.4)	2 (1.8)	7(6.3)	9 (8.0)	0.101
SLE	13 (3.9)	3 (2.7)	6 (5.4)	4 (3.6)	0.561
Liver cirrhosis	18 (5.4)	4 (3.6)	4 (3.6)	10 (8.9)	0.123
Hepatitis B	43 (12.8)	9 (8.0)	12 (10.8)	22 (19.6)	0.025
Hepatitis C	21 (6.3)	11 (9.8)	5 (4.5)	5 (4.5)	0.164
PD duration (months)	52.7 ± 41.3	46.3 ± 40.1	50.6 ± 38.8	61.1 ± 43.9	0.022
PD system (Fresenius)	7 (2.1)	1 (0.9)	2 (1.8)	4 (3.6)	0.362
PD modality (APD)	64 (19.1)	19 (17.0)	24 (21.6)	21 (18.8)	0.672
Icodextrin	176 (52.5)	54 (48.2)	60 (54.1)	62 (55.4)	0.522
Dialysate calcium (2.5mEq/L)	139 (41.5)	46 (41.1)	44 (39.6)	49 (43.8)	0.614
Residual urine	223 (67.0)	89 (80.2)	76 (68.5)	58 (52.3)	<0.001
White blood cell count (1000/μL)	7.553 ± 2.649	6.685 ± 2.354	7.619 ± 2.190	8.688 ± 2.832	<0.001
Hemoglobin (g/dL)	10.18 ± 1.53	10.37 ± 1.60	10.33 ± 1.34	9.85 ± 1.60	0.017
Platelet count (1000/μL)	249.27 ± 78.29	225.60 ± 62.67	259.50 ± 82.69	262.80 ± 82.96	<0.001
Albumin (g/dL)	4.01 ± 0.42	4.05 ± 0.40	4.03 ± 0.42	3.94 ± 0.44	0.117
Total cholesterol (mg/dL)	204.2 ± 50.3	203.3 ± 47.1	205.0 ± 50.7	204.4 ± 53.3	0.966
HDL (mg/dL)	47.2 ± 14.9	54.0 ± 15.1	44.5 ± 13.8	42.9 ± 13.5	<0.001
LDL (mg/dL)	120.1 ± 40.9	120.2 ± 40.5	120.2 ± 43.4	120.0 ± 39.3	0.999
Triglycerides (mg/dL)	183.2 ± 106.1	146.5 ± 79.2	204.5 ± 119.7	197.8 ± 106.3	<0.001
HbA1c (%)	5.61 ± 0.92	5.43 ± 0.91	5.59 ± 0.88	5.80 ± 0.95	0.011
Blood urea nitrogen (mg/dL)	58.84 ± 17.97	61.24 ± 17.48	56.32 ± 19.05	58.93 ± 17.14	0.123
Creatinine (mg/dL)	11.27 ± 2.96	11.32 ± 3.03	11.49 ± 3.19	10.99 ± 2.63	0.432
Uric acid (mg/dL)	6.83 ± 1.27	6.68 ± 1.14	6.79 ± 1.30	7.04 ± 1.35	0.096
Calcium (mg/dL)	9.99 ± 1.03	9.79 ± 1.09	10.05 ± 1.12	10.14 ± 0.84	0.027
Phosphorus (mg/dL)	4.99 ± 1.32	4.94 ± 1.18	4.99 ± 1.27	5.03 ± 1.51	0.883
Aluminum (μg/dL)	0.90 ± 0.89	0.79 ± 0.75	0.79 ± 0.79	1.11 ± 1.08	0.015
iPTH (pg/mL)	336.5 ± 383.8	299.6 ± 345.0	347.1 ± 376.6	362.9 ± 426.1	0.439
Transferrin saturation	0.272 ± 0.124	0.288 ± 0.120	0.276 ± 0.107	0.254 ± 0.141	0.115
Ferritin (μg/L)	326.0 ± 531.6	225.8 ± 349.0	304.3 ± 432.4	446.4 ± 720.0	0.010

Table 2 Peritoneal membrane characteristics of the PD patients categorized according to time-averaged serum HS-CRP levels

Time-averaged serum HS-CRP (mg/L)	Total (n = 335) 9.18 ± 12.28 (0.25 ~ 109.47)	Lower tertile (n= 112) 1.38 ± 0.67 (0.25 ~ 2.65)	Middle tertile (n = 111) 5.07 ± 1.69 (2.66~ 8.55)	Upper tertile (n = 112) 21.05 ± 15.16 (8.58 ~ 109.47)	P-value
Dialysate/plasma creatinine	0.63 ± 0.12	0.62 ± 0.11	0.64 ± 0.12	0.64 ± 0.12	0.149
Peritoneal equilibration test					0.087
High	19 (5.7)	2 (1.8)	8 (7.2)	9 (8.1)	0.091
High average	117 (35.1)	37 (33.3)	45 (40.5)	35 (31.5)	0.331
Low average	154 (46.2)	52 (46.8)	45 (40.5)	57 (51.4)	0.268
Low	43 (12.9)	20 (18.0)	13 (11.7)	10 (9.0)	0.121
Weekly Kt/V urea (total)	2.19 ± 0.38	2.21 ± 0.38	2.19 ± 0.38	2.16 ± 0.39	0.587
Weekly CCr (normalized)	61.1 ± 15.0	62.3 ± 17.2	61.2 ± 15.2	59.7 ± 12.0	0.422

Table 3 Clinical outcomes in the PD patients categorized according to time-averaged serum HS-CRP levels

Time-averaged serum HS-CRP (mg/L)	Total (n = 335) 9.18 ± 12.28 (0.25 ~ 109.47)	Lower tertile (n= 112) 1.38 ± 0.67 (0.25 ~ 2.65)	Middle tertile (n = 111) 5.07 ± 1.69 (2.66~ 8.55)	Upper tertile (n = 112) 21.05 ± 15.16 (8.58 ~ 109.47)	P-value
Outcomes					<0.001
Death	52 (15.5)	6 (5.4)	15 (13.5)	31 (27.7)	<0.001
Infection	31 (9.3)	3 (2.7)	9 (8.1)	19 (17.0)	0.001
Cardiovascular event	10 (3.0)	1 (0.9)	4 (3.6)	5 (4.5)	0.261
Malignancy	5 (1.5)	0 (0)	1 (0.9)	4 (3.6)	0.072
Sudden death	6 (1.8)	2 (1.8)	1 (0.9)	3 (2.7)	0.606
Transfer to HD	100 (29.9)	32 (28.6)	35 (31.5)	33 (29.5)	0.885
CAPD peritonitis	63 (18.8)	19 (17.0)	23 (20.7)	21 (18.8)	0.773
Membrane failure	8 (2.4)	3 (2.7)	5 (4.5)	0 (0)	0.086
EPS	16 (4.8)	4 (3.6)	5 (4.5)	7 (6.3)	0.634
Abdominal operation	7 (2.1)	4 (3.6)	2 (1.8)	1 (0.9)	0.362
Mechanical complication	2 (0.6)	1 (0.9)	0 (0)	1 (0.9)	0.607
ADL disability	4 (1.2)	1 (0.9)	0 (0)	3 (2.7)	0.172
Transplantation	12 (3.6)	2 (1.8)	8 (7.2)	2 (1.8)	0.043
Technique survival	171 (51.0)	72 (64.3)	53 (47.7)	46 (41.1)	0.002
Cardiovascular event(s)	91 (27.2)	20 (17.9)	29 (26.1)	42 (37.5)	0.004
Infection episode(s)	221 (66.0)	64 (57.1)	73 (65.8)	84 (75.0)	0.019
Malignancy	35 (10.4)	9 (8.0)	8 (7.2)	18 (16.1)	0.057
Urothelial cell carcinoma	11 (3.3)	3 (2.7)	4 (3.6)	4 (3.6)	0.908
Renal cell carcinoma	7 (2.1)	2 (1.8)	3 (2.7)	2 (1.8)	0.859
Breast cancer	4 (1.2)	1 (0.9)	0 (0)	3 (2.7)	0.172
Thyroid cancer	4 (1.2)	1 (0.9)	1 (0.9)	2 (1.8)	0.779
Hepatocellular carcinoma	2 (0.6)	0 (0)	0 (0)	2 (1.8)	0.135
Gynecologic cancer	2 (0.6)	1 (0.9)	0 (0)	1 (0.9)	0.607
Prostate cancer	1 (0.3)	1 (0.9)	0 (0)	0 (0)	0.368
Lung cancer	1 (0.3)	0 (0)	0 (0)	1 (0.9)	0.368
Rectal cancer	2 (0.6)	0 (0)	0 (0)	2 (1.8)	0.135
Brain glioma	1 (0.3)	0 (0)	0 (0)	1 (0.9)	0.368
EPS	16 (4.8)	4 (3.6)	5 (4.5)	7 (6.3)	0.634

Notes: Categorical variables are given as number (percentage).

Table 4 Hazard ratio of mortality in univariate and multivariate Cox regression analysis

	Univariate HR	95% CI	P-value	Multivariate (enter method) HR	95% CI	P-value
Baseline serum HS-CRP (mg/L)	1.018	1.007–1.028	0.001	0.984	0.961–1.008	0.187
Time-averaged serum HS-CRP (mg/L)	1.037	1.025–1.050	<0.001	1.028	1.001–1.056	0.044
Male	1.005	0.563–1.795	0.986			
Age (years)	1.083	1.059–1.108	<0.001	1.066	1.036–1.096	<0.001
Body mass index (Kg/m²)	1.058	0.986–1.135	0.116			
DM	4.182	2.373–7.370	<0.001	1.477	0.614–3.554	0.384
CAD	4.266	1.535–11.853	0.005	1.456	0.418–5.073	0.555
CHF	0.671	0.163–2.758	0.580			
Stroke	3.120	1.407–6.923	0.005	1.397	0.536–3.641	0.494
SLE	0.460	0.064–3.327	0.442			
Liver cirrhosis	1.885	0.749–4.744	0.178			
Hepatitis B	0.888	0.379–2.079	0.784			
Hepatitis C	1.627	0.647–4.093	0.301			
PD duration (months)	0.997	0.990–1.005	0.494			
Residual urine	0.544	0.313–0.945	0.031	0.730	0.389–1.373	0.329
White blood cell count (1000/uL)	1.054	0.963–1.154	0.250			
Hemoglobin (g/dL)	0.853	0.716–1.017	0.077			
Platelet count (1000/uL)	0.998	0.995–1.002	0.416			
Albumin (g/dL)	0.397	0.227–0.691	0.001	0.575	0.231–1.432	0.235
Total cholesterol (mg/dL)	0.998	0.993–1.004	0.527			
HDL (mg/dL)	0.991	0.971–1.012	0.399			
LDL (mg/dL)	0.996	0.988–1.003	0.277			
Triglyceride (mg/dL)	1.001	0.999–1.003	0.391			
HbA1c (%)	1.456	1.209–1.753	<0.001	1.028	0.694–1.523	0.889
Blood urine nitrogen (mg/dL)	0.998	0.983–1.014	0.842			
Creatinine (mg/dL)	0.905	0.820–0.999	0.048	1.119	0.987–1.268	0.080
Uric acid (mg/dL)	1.085	0.874–1.346	0.462			
Calcium (mg/dL)	0.845	0.650–1.099	0.208			
Phosphorus (mg/dL)	0.906	0.732–1.120	0.360			
Aluminum (μg/dL)	0.921	0.643–1.319	0.653			
iPTH (pg/mL)	1.000	0.999–1.000	0.403			
Transferrin saturation	0.033	0.002–0.589	0.020	0.083	0.004–1.948	0.122
Ferritin (μg/L)	1.000	1.000–1.001	0.350			
PD system (Fresenius Stay Safe)	0.902	0.125–6.529	0.919			
PD modality (APD)	1.439	0.754–2.743	0.270			
Icodextrin	0.625	0.360–1.083	0.094			
Dialysate calcium (2.5mEq/L)	1.114	0.677–1.833	0.671			
Dialysate/plasma creatinine	13.239	1.386–126.46	0.025	2.703	0.175–41.773	0.477
Weekly Kt/V urea (total)	0.442	0.200–1.003	0.053			
Weekly CCr (normalized)	0.977	0.956–1.012	0.062			
Cardiovascular event(s)	4.792	2.750–8.350	<0.001	2.092	1.086–4.028	0.027
Infection episode(s)	2.093	1.097–3.993	0.025	1.110	0.558–2.206	0.766

Table 5 Hazard ratio of dropout (transplantation censored) in univariate and multivariate Cox regression analysis

	Univariate HR	95% CI	P-value	Multivariate (enter method) HR	95% CI	P-value
Baseline serum HS-CRP (mg/L)	1.008	1.001–1.017	0.048	1.010	0.995–1.026	0.203
Time-averaged serum HS-CRP (mg/L)	1.024	1.015–1.034	<0.001	1.013	1.001–1.027	0.042
Male	1.060	0.756–1.487	0.735			
Age (years)	1.028	1.014–1.041	<0.001	1.012	0.995–1.029	0.170
Body mass index (Kg/m²)	0.989	0.946–1.035	0.642			
DM	1.895	1.282–2.802	0.001	1.244	0.674–2.296	0.485
CAD	2.478	1.159–5.295	0.019	1.371	0.568–3.310	0.482
CHF	1.202	0.633–2.282	0.575			
Stroke	1.703	0.944–3.073	0.077			
SLE	0.500	0.159–1.568	0.235			
Liver cirrhosis	1.535	0.851–2.771	0.155			
Hepatitis B	1.198	0.768–1.867	0.425			
Hepatitis C	1.411	0.799–2.492	0.235			
PD duration (months)	1.006	1.003–1.010	<0.001	1.000	0.994–1.006	0.939
Residual urine	0.639	0.461–0.886	0.007	0.948	0.592–1.516	0.823
White blood cell count (1000/uL)	1.032	0.977–1.091	0.259			
Hemoglobin (g/dL)	0.871	0.785–0.966	0.009	0.954	0.838–1.086	0.478
Platelet coutn (1000/uL)	1.001	0.999–1.003	0.351			
Albumin (g/dL)	0.566	0.399–0.804	0.001	0.747	0.439–1.272	0.283
Total cholesterol (mg/dL)	0.999	0.996–1.002	0.441			
Triglyceride (mg/dL)	1.000	0.998–1.001	0.907			
HDL (mg/dL)	1.000	0.988–1.012	0.966			
LDL (mg/dL)	0.998	0.994–1.003	0.398			
HbA1c (%)	1.168	1.007–1.355	0.040	0.953	0.742–1.224	0.707
Blood urine nitrogen (mg/dL)	0.992	0.982–1.001	0.087			
Creatinine (mg/dL)	0.950	0.898–1.004	0.070			
Uric acid (mg/dL)	0.920	0.806–1.052	0.223			
Calcium (mg/dL)	0.999	0.852–1.172	0.994			
Phosphorus (mg/dL)	0.915	0.809–1.035	0.159			
Aluminum (μg/dL)	1.183	1.005–1.394	0.044	1.062	0.875–1.289	0.541
iPTH (pg/mL)	1.000	0.999–1.000	0.679			
Transferrin saturation	0.458	0.113–1.863	0.275			
Ferritin (μg/L)	1.000	1.000–1.000	0.144			
PD system (Fresenius Stay Safe)	0.580	0.144–2.341	0.444			
PD modality (APD)	1.297	0.878–1.916	0.191			
Icodextrin	0.762	0.554–1.047	0.094			
Dialysate calcium (2.5mEq/L)	0.953	0.708–1.282	0.750			
Dialysate/plasma creatinine	7.680	2.037–28.954	0.003	1.255	0.190–8.304	0.814
Weekly Kt/V urea (total)	0.939	0.608–1.450	0.775			
Weekly CCr (normalized)	0.993	0.982–1.005	0.235			
Cardiovascular event(s)	1.853	1.331–2.579	<0.001	1.466	0.966–2.225	0.072
Infection episode(s)	2.843	1.874–4.312	<0.001	2.129	1.335–3.397	0.002
Malignancy	1.478	0.941–2.323	0.090			
EPS	2.519	1.497–4.237	<0.001	2.296	1.446–4.331	0.015

Figure 1 Comparison of the cumulative patient survival during the 5-year follow-up.
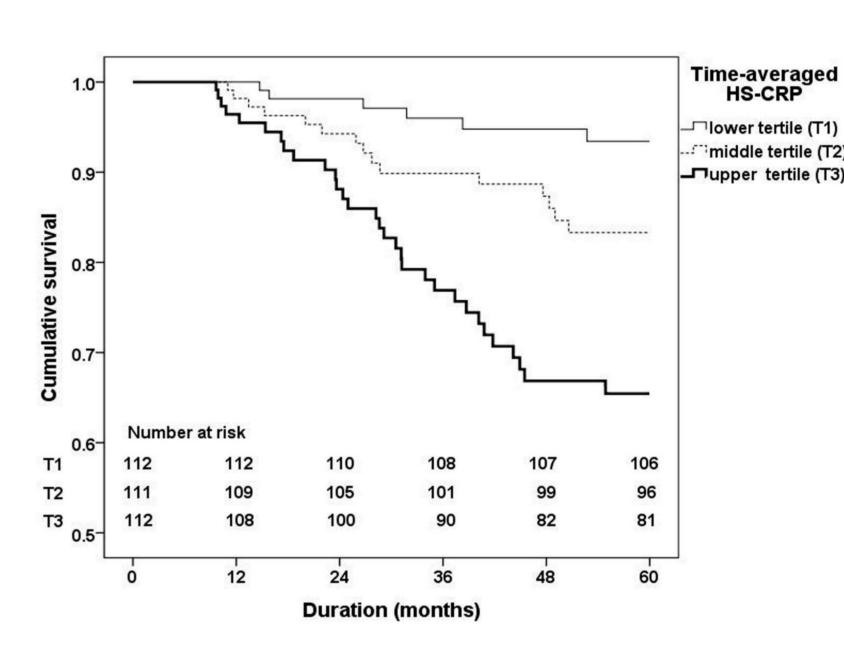

Figure 2 Comparison of the cumulative technique survival (transplantation censored) during the 5-year follow-up.
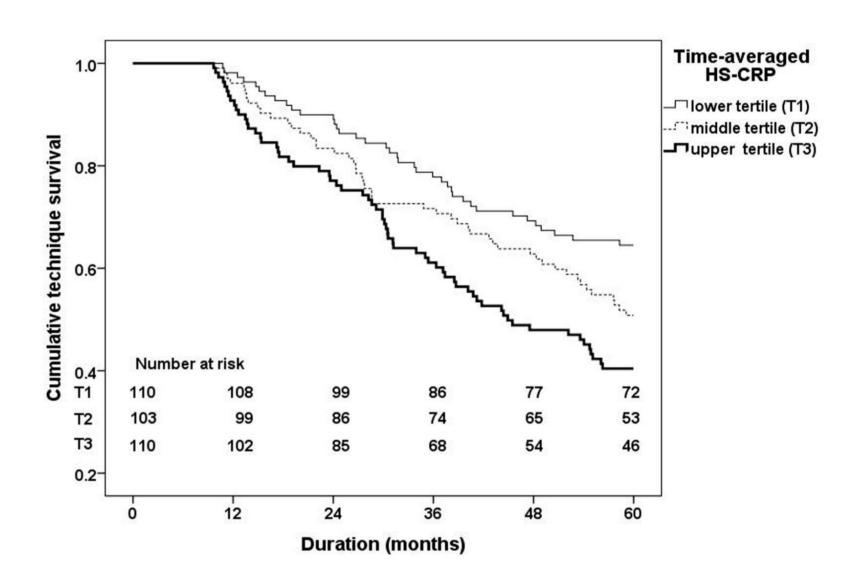

Figure 3 ROC curve analysis for predictability of mortality between the time-averaged and baseline HS-CRP levels.
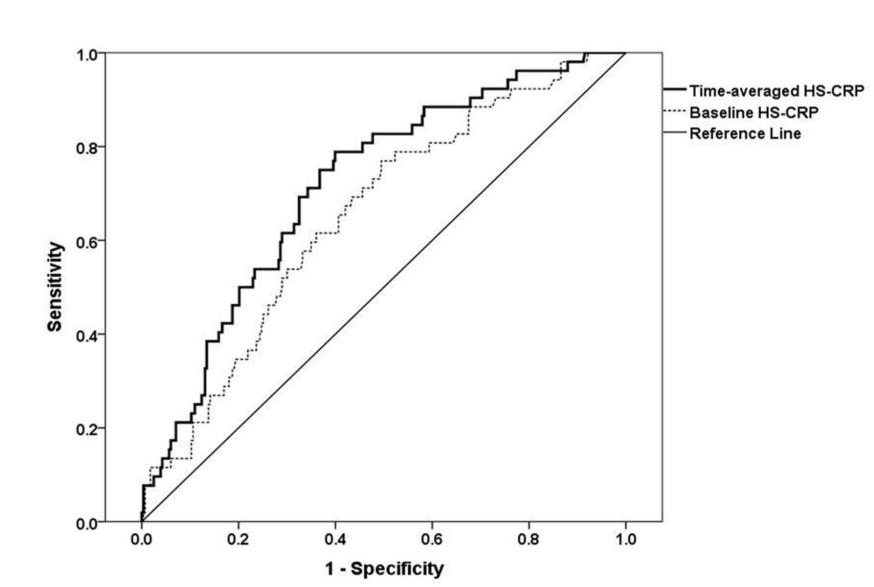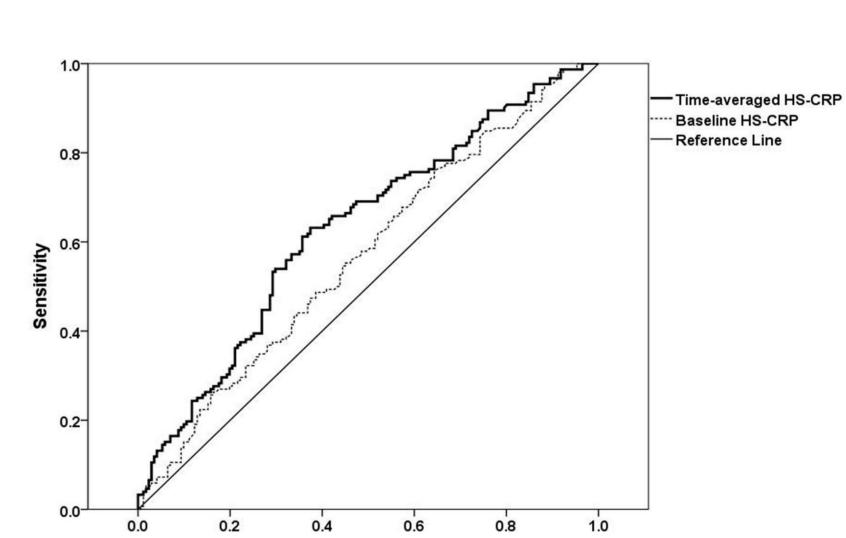

Figure 4 ROC curve analysis for predictability of dropout between the time-averaged and baseline HS-CRP levels.

Summary

During 5-year follow-up, 164 of 335 patients (49.0%) ceased PD, including 52 who died (15.5%), 100 (29.9%) who converted to hemodialysis, and 12 (3.6%) who underwent kidney transplantation. The Kaplan–Meier analysis and log-rank test results demonstrated a significant difference in the cumulative patient survival rate across the 3 tertiles (the lowest rate in upper tertile). In a multivariate Cox regression analysis, only a higher time-averaged serum HS-CRP level, older age, and the occurrence of cardiovascular events were identified as independent predictors of mortality. Every 1 mg/L increase in time-averaged serum HS-CRP level was independently predictive of a 2.8% increase in mortality. Multivariate Cox regression analysis showed that a higher time-averaged serum HS-CRP level, the occurrence of infection episodes and EPS were independent predictors of dropout.

Conclusions

The present study shows the time-averaged serum HS-CRP level is superior to a single baseline measurement in predicting the 5-year mortality and dropout in PD patients.

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