# THE INTERDIALYTIC PERIOD FOR BLOOD COLLECTION INFLUENCES SERUM PHOSPHORUS AND THE RISK OF MORTALITY IN THE COSMOS STUDY

Adriana Dusso[1], José Luis Fernández-Martín[1], Pablo Martínez-Camblor[2], Maria Paula Dionisi[1], Jürgen Floege[2], Markus Ketteler[2], Gérard London[2], Francesco Locatelli[2], José Luis Gorriz[2], Boleslaw Rutkowski[2], Willem-Jan Bos[2], Christian Tielemans[2], Pierre-Yves Martin[2], Rudolf P. Wüthrich[2], Drasko Pavlovic[2], Miha Benedik[2], Diego Rodríguez-Puyol[2], Juan Jesús Carrero[2], Carmine Zoccali[2], Jorge B. Cannata-Andia[2] on behalf of the COSMOS group.

[1]Bone and Mineral Research Unit. Instituto Reina Sofía, RedinRen del ISCIII, Hospital Universitario Central de Asturias, Oviedo, Asturias, Spain and [2]COSMOS group.
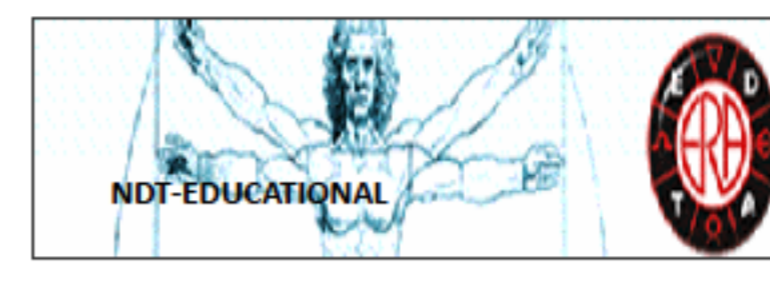
INTRODUCTION AND AIMS: Phosphorus (P), calcium (Ca) and PTH are the main serum biochemical parameters of bone and mineral metabolism used for the current management of Chronic Kidney Disease-Mineral and Bone Disorders (CKD-MBD). This study assessed the influence of the two days (midweek, MW) or three days (post-weekend, PW) dialysis interval for blood withdrawal on serum levels of CKD-MBD biochemical parameters, their potential implications for treatment and their association with mortality.

METHODS: COSMOS is a 3-year, observational, open-cohort, prospective study including patients from 227 centres in 20 European countries. Demographics, comorbidities, treatments and biochemical parameters of the previous 6 months were collected at baseline and every 6 months. The COSMOS cohort (6797 patients, CKD stage 5D) was divided into two groups, depending on whether their centres withdrew blood MW or PW, to assess differences in serum CKD-MBD parameters and all-cause mortality. Three progressive Cox' multivariate models were used to adjust the Hazard Ratio. Model 1: demographics and comorbidities (10 parameters), Model 2: Model 1 plus treatments (18 parameters) and Model 3: Model 2 plus biochemical parameters (22 parameters). All multivariate models were stratified by centre.

RESULTS: There were no differences in serum Ca or PTH levels between MW and PW patients. In contrast, PW patients showed higher serum P than MW patients (5.5 ± 1.4 vs. 5.2 ± 1.4 mg/dL, p<0.001, Table 1) in univariate and multivariate analyses and a significantly higher percentage of patients with serum P above the upper KDOQI (PW=45.2% vs. MW= 37.6%) target (5.5 mg/dL). Despite these differences, the prescription of phosphate binders was similar in both groups (MW: 84.8%; PW: 85.0%, p=0.9).

The time of blood withdrawal also influenced the relative risk of mortality in relation to serum P. The lowest mortality ranges (Hazard ratio ≤ 1.1) for serum P were 3.5 to 4.9 mg/dL (95% CI: 2.9-5.2 mg/dL) when sampled MW (Fig.1, Left Panel) and 3.8 to 5.7 mg/dL (95% CI: 3.0-6.4 mg/dL) when sampled PW (Fig 1, Right Panel). Also, the association between high serum P and mortality risk was stronger for MW serum P measurements (Fig.1, Middle Panel). For serum P within the 5.5 to 6.3 mg/dL range (quintile 4), MW collection was associated with a higher relative risk of mortality (HR=1.35 [95% CI: 1.01-1.82], p=0.047) compared with PW suggesting that MW values may better reflect the actual exposure to high serum P .

Table 1- Baseline characteristics of the full cohort of patients.

|	All patients		Midweek		Post-weekend	p-value*
Demographics & comorbidities						
Sex (Men) (n, %)	6679	60.5	3139	60.3	3540	60.7	0.8
Age (years) (n, mean±SD)	6679	64.1±14.4	3139	63.6±14.6	3540	64.5±14.2	0.016
Body Mass Index (kg/m²) (n, mean±SD)	6673	25.4±5.1	3138	25.3±5.2	3535	25.4±4.9	0.3
Current smokers (%)	6674	13.8	3139	12.9	3535	14.5	0.07
Diabetes Mellitus (n, %)	6678	31.1	3139	29.3	3539	32.6	0.004
History of cardiovascular disease (n, %)	6675	71.7	3139	71.8	3536	71.7	1.0
Parathyroidectomy (n, %)	6679	4.8	3139	4.1	3540	5.5	0.011
Vintage (months) (n, mean±SD)	6679	38.2±49.0	3139	39.0±50.4	3540	37.5±47.8	0.2
Treatments						
Time of Dialysis (hours per week) (n, mean±SD)	6679	12.0±2.1	3139	11.9±2.1	3540	12.1±2.2	<0.001
Type of Haemodialysis (n)	6678		3138		3540		<0.001
Conventional low flux (%)		53.5		49.8		56.8	
Conventional high flux (%)		37.4		41.0		34.1	
Hemodiafiltration & Other (%)		9.1		9.2		9.1	
Calcium conc. in the dialysate (mEq/L)† (n)	6004		2733		3271		<0.001
2.5 (%)		29.6		28.4		30.6	
3.0 (%)		51.4		48.1		54.1	
3.5 (%)		19.1		23.5		15.3	
Treatment with phosphate binders (n, %)	6678	84.9	3139	84.8	3539	85.0	0.9
Treatment with active vitamin D (n, %)	6676	47.7	3137	45.0	3539	50.1	<0.001
Treatment with calcimimetics (n, %)	6629	6.2	3091	6.8	3538	5.8	0.1
Treatment with ESAs (n, %)	6511	90.8	2989	90.7	3512	90.8	0.9
Biochemical parameters						
Serum phosphorus (mg/dL) (n, mean±SD)	6679	5.4±1.4	3139	5.2±1.4	3540	5.5±1.4	<0.001
Serum PTH (pg/mL) (n, median[IQR])	6374	200.1 [102.5-369.2]	2952	203.0 [103.5-384.6]	3422	199.0 [101.7-351.5]	0.047†
Serum Ca (mg/dL) (n, mean±SD)	6432	9.1±0.7	3002	9.1±0.8	3340	9.1±0.7	0.5
Serum Albumin (g/dL) (n, mean±SD)	6009	3.8±0.5	2896	3.7±0.5	3113	3.8±0.4	<0.001
Haemoglobin (g/dL) (n, mean±SD)	6597	11.4±1.4	3084	11.4±1.4	3513	11.5±1.3	0.2

For **Demographic and Treatment Variables**, values indicate mean ± SD (standard deviation) or % of patients. n: number of patients.
*Student's t-test for continuous variables and chi-square test for categorical variables were used. ESAS: Erythropoietin Stimulating Agents
For **Biochemical Parameters**, values are expressed as mean ± SD or median [lower and upper limits of IQR] according to normal and non-normal distribution, respectively. n: number of patients, IQR: Interquartil range. *Student's t-test. †Mann-Whitney U Test.

Fig.1- Association between all-cause mortality and serum phosphorus in midweek and post-weekend patients.
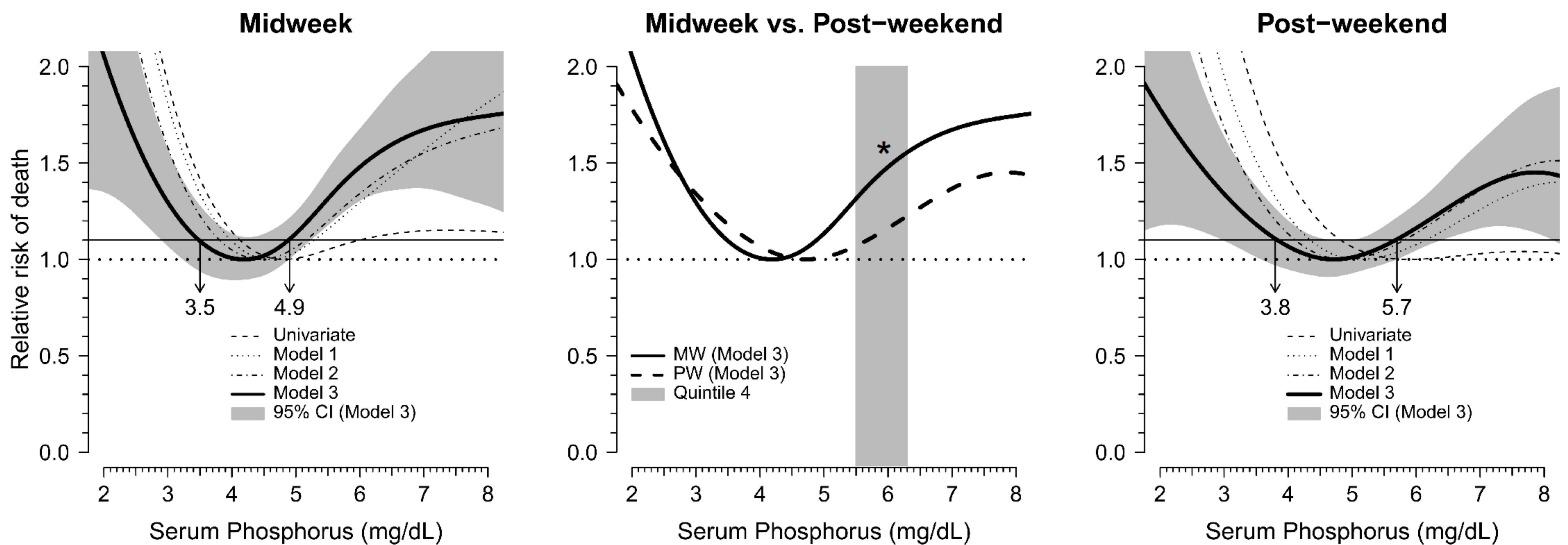
The middle panel shows the comparison between midweek (left panel) and post-weekend patients (right panel) when using the full adjusted model. Arrows show the serum phosphorus with the lowest mortality ranges (less than 10% increase in the relative risk of mortality, HR=1.1). The grey bar in the middle panel shows that for serum P within the 5.5 to 6.3 mg/dL range (quintile 4), MW collection was associated with a higher relative risk of mortality (HR=1.35 [95% CI: 1.01-1.82], *p=0.047)) compared with PW.

Fig. 2- Comparison of KDOQI and KDIGO recommended targets for serum P with COSMOS midweek and post-weekend lowest mortality ranges.
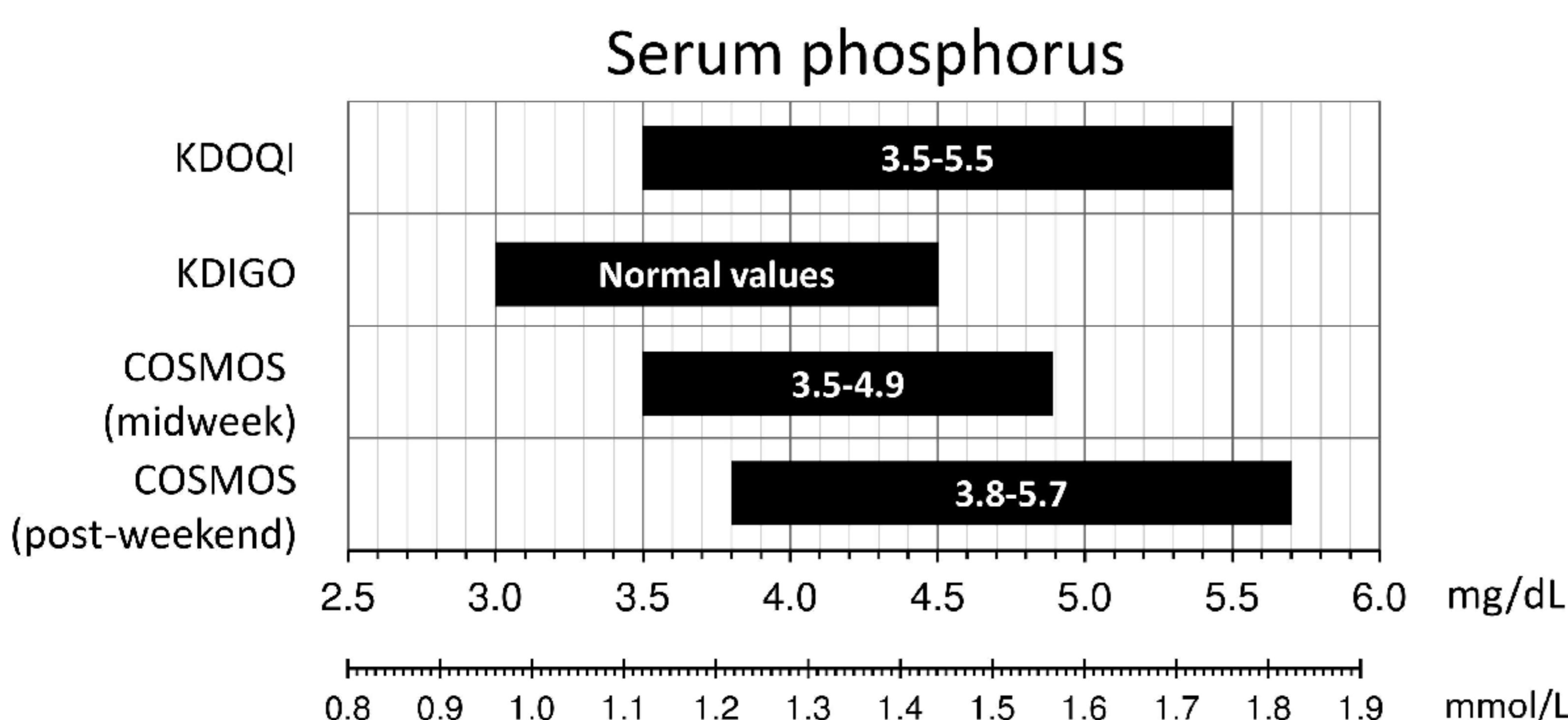
CONCLUSIONS:
- A 3 days interdialytic period for blood withdrawal (PW) results in significantly higher serum P levels compared to MW measurements.
- MW serum P values associate with a higher risk of mortality compared to PW values, suggesting that they better reflect the patient exposure to high serum P.
- Future clinical guidelines recommending optimal serum target ranges for P and therapeutic strategies for P control should consider the timing of blood withdrawal (Fig. 2).