Research Square

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Concurrent Changes in Serum Butyrylcholinesterase and Prescribed Phosphate-Lowering Medication Intensity in Maintenance Hemodialysis: An Exploratory Longitudinal Study

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Research Article

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Abstract

Background

Prescribed phosphate-lowering therapy reflects both laboratory results and clinical decisions in maintenance hemodialysis. Whether changes in a study-specific prescription intensity score accompany changes in serum butyrylcholinesterase (BChE) is unknown. We explored this association without assuming that the score measures dietary intake.

Methods

This retrospective longitudinal study included 110 adults receiving thrice-weekly hemodialysis for 16 months. The primary analysis evaluated the contemporaneous association between 3-month changes in post-laboratory P-index and BChE using interval fixed effects and patient-clustered robust standard errors. Albumin was the comparator, and a lagged model examined whether prior P-index predicted next-quarter BChE.

Results

A 6-point P-index increase was associated with a 2.04% contemporaneous BChE increase after adjustment for normalized protein catabolic rate (nPCR), phosphorus, inflammation, volume status, dialysis dose, and mineral-bone variables (95% confidence interval [CI] 0.65–3.46%; P = 0.004). The corresponding albumin association was 0.41% (95% CI -0.53 to 1.36%; P = 0.393), and the association was stronger for BChE than albumin (difference 1.63 percentage points; 95% CI 0.51–2.76; P for interaction = 0.005). Prior P-index did not clearly predict next-quarter BChE (0.35%; 95% CI -0.02 to 0.72%; P = 0.067).

Conclusions

Changes in BChE and prescribed phosphate-lowering intensity were associated over the same interval, whereas the lagged association was inconclusive. The score is unvalidated and the findings do not establish temporal direction, dietary intake, medication effects, or clinical utility.

Background

Nutritional assessment in maintenance hemodialysis is multidimensional because no single measure captures dietary intake, inflammation, fluid distribution, and body-composition change. Guidelines therefore recommend serial assessment using dietary, biochemical, and anthropometric information [1]. Albumin is widely used but is influenced by inflammation and volume status [2, 3].

Serum butyrylcholinesterase (BChE) is a liver-synthesized protein associated with protein-energy status and prognosis in kidney disease [4, 5]. A previous longitudinal study found that BChE change was associated with prescribed dry-weight change after accounting for inflammation and volume-related change [6]. Whether BChE also tracks information related to protein intake and phosphorus management is uncertain.

Normalized protein catabolic rate (nPCR) is an intake-related measure in metabolically stable dialysis patients, whereas serum phosphorus is affected by diet, dialysis removal, mineral metabolism, medications, and adherence [1, 7–10]. Prescribed phosphate-lowering medication requirement may integrate serial phosphorus values and clinicians' treatment responses, but also reflects potency, tolerance, pill burden, adherence, and practice style [11–14]. It is therefore not a direct measure of dietary intake or medication ingestion.

We explored whether within-patient changes in BChE accompanied changes in a study-specific score of prescribed phosphate-lowering intensity in routine practice. Associations with nPCR and phosphorus, comparisons with albumin, and a lagged analysis were secondary or exploratory. This observational study was not designed to validate the score as a measure of intake or to establish clinical utility.

Methods

Study design and participants

This retrospective longitudinal study was conducted at a single dialysis center in Japan from September 2024 through December 2025. Eligible adults received maintenance dialysis continuously throughout the study period. Patients with documented liver cirrhosis or a change in dialysis frequency were excluded. All included patients received dialysis three times weekly without a modality change. Residual kidney function and urine output were not measured. Sex was obtained from medical records. All eligible patients were included without a formal sample-size calculation.

The cohort and observation period overlapped with a previous report on BChE and prescribed dry-weight change [6]. The present study addressed a distinct question using phosphorus-management measures and different primary analyses.

Measurements

Monthly measurements included BChE, albumin, human atrial natriuretic peptide (hANP), C-reactive protein (CRP), single-pool Kt/V, geriatric nutritional risk index, nPCR, phosphorus, total calcium, intact parathyroid hormone (PTH), total alkaline phosphatase (ALP), and prescribed phosphate-lowering medications. Predialysis samples were obtained before a midweek session; hANP was measured immediately before blood return at the end of that session. BChE was measured by the p-

hydroxybenzoylcholine/NADPH ultraviolet method on a cobas c 703 analyzer (Roche Diagnostics); the reference interval was 240–486 U/L.

Calculation of Kt/V and nPCR

Single-pool Kt/V and nPCR were calculated using the Shinzato equations from paired pre- and postdialysis blood urea nitrogen and routine treatment data from the same midweek session [15]. nPCR was expressed in g/kg/day.

Phosphate-lowering medication indices

The target predialysis phosphorus range was 3.5-6.0 mg/dL. Dose escalation was generally considered after repeated values above 6.0 mg/dL and reduction below 3.5 mg/dL, but decisions also considered calcium, PTH, gastrointestinal symptoms, tolerability, pill burden, and clinically assessed adherence. Neither BChE nor nPCR guided prescriptions. Each monthly medication record represented the regimen prescribed after review of that month's laboratory results.

We developed a study-specific semiquantitative P-index because agents differed in formulation, dose, mechanism, and expected potency (Table 1). Standardized daily-dose blocks were multiplied by agent-specific weights and summed; an unweighted medication burden was also calculated.

Conventional binder weights were anchored to published phosphate-binder equivalent doses [16], and weights for iron-based binders and tenapanor were informed by Japanese comparative and dose-response studies [17–22]. Six points represented a prespecified scaling unit for reporting, not a validated clinically meaningful difference or an exact or universal phosphorus reduction. Tenapanor was weighted by its observed phosphorus-lowering effect because it is not a binder. Higher scores indicated greater prescribed intensity, not confirmed ingestion or a causal medication effect.

Exploratory analyses evaluated an equal-weight phosphorus/P-index composite, a phosphorus × P-index product, and a centered phosphorus-by-P-index interaction.

Table 1
Construction of the P-index

Phosphate-lowering agent	Reference daily regimen	P-index points	Regimen corresponding to 6 points
Tenapanor	5 mg twice daily	6	10 mg/day
Lanthanum carbonate	250 mg three times daily	6	750 mg/day
Sucroferric oxyhydroxide	250 mg three times daily	6	750 mg/day
Ferric citrate hydrate	250 mg three times daily	3	1,500 mg/day
Calcium carbonate	250 mg three times daily	3	1,500 mg/day
Sevelamer hydrochloride	250 mg three times daily	2	2,250 mg/day

Medication variables represent standardized daily-dose blocks rather than tablet counts. Scores were scaled to dose and summed across agents. Tenapanor was weighted by observed phosphorus lowering rather than binding capacity. P-index is study-specific and does not represent confirmed ingestion or exact drug equivalence.

Analysis windows

Five nonoverlapping 3-month mean periods yielded 550 possible patient-periods; 548 were complete for mean nPCR models. Five consecutive 3-month endpoint changes yielded 550 possible intervals; 547 were complete for the fully adjusted primary model. The primary analysis was the adjusted within-patient association between same-interval changes in post-laboratory P-index and BChE. nPCR, phosphorus, albumin comparisons, temporal models, and sensitivity analyses were secondary or exploratory. The analytic framework was not preregistered.

Use of generative artificial intelligence: During preparation of this work, the authors used ChatGPT (OpenAI) to assist with translation, English-language editing, and review of statistical code. The authors reviewed and edited all outputs, performed and verified the analyses, and take full responsibility for the article.

Statistical analysis

Continuous data are reported as mean ± standard deviation or median [interquartile range], and categorical data as number (percentage). BChE, albumin, hANP, CRP, PTH, and total ALP were log10-

transformed. Coefficients for log10 outcomes were converted to percentage differences as 100 × (10^β − 1).

Models of 3-month means used patient and period fixed effects with patient-clustered, small-sample-corrected robust standard errors. The core nPCR model adjusted for CRP, hANP, and Kt/V; phosphorus and P-index were added in a sensitivity model. Quarterly-change models used interval fixed effects and the same robust covariance approach. The primary P-index model adjusted for sex and concurrent changes in nPCR, phosphorus, CRP, hANP, Kt/V, total calcium, PTH, and total ALP. Equivalent models were fitted for albumin, and stacked interacted models compared associations between outcomes.

Temporal models evaluated prior phosphorus in relation to subsequent P-index and prior P-index in relation to next-quarter BChE, with prior outcome and clinical covariates. Sensitivity analyses examined alternative calcium specifications, baseline adjustment, nonlinearity, nonzero P-index changes, outliers, inflammation, unweighted burden, tenapanor exclusions, and leave-one-patient-out estimates. Mean analyses required all three monthly measurements; change analyses required both endpoints, and other missing covariates were handled by complete-case analysis. Inference used patient-clustered finite-sample correction and G − 1 degrees of freedom. Tests were two-sided with alpha = 0.05; secondary and exploratory analyses were not multiplicity-adjusted. Analyses used Python 3.12.13, pandas 2.2.3, NumPy 2.3.5, SciPy 1.17.0, and statsmodels 0.14.5.

Results

Cohort characteristics

Among 143 adults treated during the study period, 17 initiated dialysis after study entry and 13 transferred before completion. Of 113 continuously treated patients, two with cirrhosis and one with changed dialysis frequency were excluded, leaving 110 participants and 1,760 monthly observations (Fig. 1). Mean age was 71.8 years and 85 participants (77.3%) were male (Table 2). Of 550 quarterly intervals, 547 were complete for the primary model.

Table 2
Baseline Characteristics of the Study Cohort

Characteristic	Value (N = 110)
Age, y	71.8 ± 12.3
Male sex, n (%)	85 (77.3)
Diabetes, n (%)	54 (49.1)
Hemodiafiltration (I-HDF or online HDF), n (%)	73 (66.4)
Dialysis vintage, mo	63.0 [35.0–99.8]
Serum butyrylcholinesterase, U/L	205.5 [169.3–252.5]
Albumin, g/dL	3.6 [3.2–3.8]
hANP, pg/mL	52.0 [28.6–88.4]
CRP, mg/dL	0.18 [0.06–0.39]
Single-pool Kt/V	1.41 [1.31–1.55]
GNRI	93.8 [87.9–96.8]
nPCR, g/kg/day	0.80 [0.70–0.90]
Serum phosphorus, mg/dL	4.7 [3.9–5.6]
P-index, points	12 [0–18]
Unweighted medication burden, blocks	2 [0–4]
Calcium, mg/dL	8.6 [8.2–9.1]
Intact PTH, pg/mL	105 [52–168]
Total ALP, U/L	69 [54–89]

Values are mean ± standard deviation, median [interquartile range], or n (%). N = 110 unless indicated. ALP, alkaline phosphatase; CRP, C-reactive protein; GNRI, geriatric nutritional risk index; hANP, human atrial natriuretic peptide; nPCR, normalized protein catabolic rate; PTH, parathyroid hormone.

nPCR, phosphorus, and BChE

Within patients, a 0.1-g/kg/day higher 3-month mean nPCR was associated with 3.09% higher BChE (95% CI 1.77–4.42%; P < 0.001). The estimate was 2.64% after CRP adjustment but attenuated to 0.57% after additional adjustment for hANP and Kt/V (95% CI -0.84 to 2.00%; P = 0.429) (Table 3).

A 0.1-g/kg/day quarterly nPCR increase was associated with a 0.422-mg/dL adjusted phosphorus increase (95% CI 0.310–0.534; P < 0.001). Phosphorus change was not independently associated with

BChE change (0.76% per 1 mg/dL; 95% CI -0.28 to 1.81%; P = 0.152), nor was adjusted nPCR change (0.04% per 0.1 g/kg/day; 95% CI -0.92 to 1.01%; P = 0.933).

Table 3
Key Longitudinal Associations Across Nutrition- and Phosphorus-Management Measures

Association	Scale	Estimate	95% CI	P	Model (N)
Mean nPCR with mean BChE	Per 0.1 g/kg/day	+ 3.09%	1.77% to 4.42%	< .001	Patient + period FE (N = 548)
Mean nPCR with mean BChE	Per 0.1 g/kg/day	+ 0.57%	-0.84% to 2.00%	.429	Core-adjusted FE (N = 548)
ΔnPCR with Δphosphorus	Per 0.1 g/kg/day	+ 0.422 mg/dL	0.310 to 0.534	< .001	Model A (N = 547)
Δphosphorus with ΔBChE	Per 1 mg/dL	+ 0.76%	-0.28% to 1.81%	.152	Model B (N = 547)
ΔP-index with ΔBChE	Per 6 points	+ 2.04%	0.65% to 3.46%	.004	Primary model (N = 547)
Δunweighted burden with ΔBChE	Per 1 block	+ 1.44%	0.49% to 2.40%	.003	Core burden model (N = 550)
Prior mean P-index with next mean BChE	Per 6 points	+ 0.35%	-0.02% to 0.72%	.067	Temporal model (N = 438)

Mean models used patient and period fixed effects (FE); core adjustment added log10 CRP, log10 hANP, and Kt/V. Quarterly models used interval FE. The primary model adjusted for sex and changes in nPCR, phosphorus, log10 CRP, log10 hANP, Kt/V, total calcium, log10 PTH, and log10 total ALP. Model A omitted phosphorus; model B omitted P-index; the core burden model omitted mineral-bone variables. The temporal model adjusted for prior BChE, phosphorus, nPCR, log10 CRP, log10 hANP, Kt/V, and period. CI, confidence interval; Delta (Δ), 3-month change.

P-index and BChE

A 6-point quarterly P-index increase was associated with a 2.61% BChE increase (95% CI 1.11–4.13%; P < 0.001) and a 2.04% increase after full adjustment (95% CI 0.65–3.46%; P = 0.004) (Table 3). In the core-adjusted unweighted model, each additional standardized daily-dose block was associated with a 1.44% BChE increase (95% CI 0.49–2.40%; P = 0.003; 550 intervals); this model used fewer covariates than the primary model. The tenapanor-excluded analysis also showed a positive association. P-index increased in 58 intervals, decreased in 65, and was unchanged in 427; the 123 nonzero changes came from 68 participants (Additional file 1: Table S1).

Comparison with albumin

A 0.1-g/kg/day higher mean nPCR was associated with 1.42% higher albumin (95% CI 0.67–2.18%; P < 0.001), but the core-adjusted estimate was 0.74% (95% CI -0.01 to 1.51%; P = 0.054). The adjusted nPCR

associations did not differ between BChE and albumin (P for interaction = 0.799) (Table 4).

The adjusted association between P-index change and albumin was 0.41% per 6 points (95% CI -0.53 to 1.36%; P = 0.393). The P-index association was 1.63 percentage points stronger for BChE than albumin (95% CI 0.51–2.76; P for interaction = 0.005) (Table 4).

Table 4
Direct Comparison of BChE and Albumin

Analysis	Scale	Estimate	95% CI	P
Mean nPCR with mean BChE	Per 0.1 g/kg/day	+ 3.09%	1.77% to 4.42%	< .001
Mean nPCR with mean albumin	Per 0.1 g/kg/day	+ 1.42%	0.67% to 2.18%	< .001
Core-adjusted mean nPCR with mean BChE	Per 0.1 g/kg/day	+ 0.57%	-0.84% to 2.00%	.429
Core-adjusted mean nPCR with mean albumin	Per 0.1 g/kg/day	+ 0.74%	-0.01% to 1.51%	.054
BChE vs albumin nPCR-effect difference	Per 0.1 g/kg/day	-0.17	-1.52 to 1.19	.799
Adjusted ΔP-index with ΔBChE	Per 6 points	+ 2.04%	0.65% to 3.46%	.004
Adjusted ΔP-index with Δalbumin	Per 6 points	+ 0.41%	-0.53% to 1.36%	.393
BChE vs albumin P-index-effect difference	Per 6 points	+ 1.63	0.51 to 2.76	.005

Mean models included 548 patient-periods; quarterly P-index models included 547 patient-intervals. Core mean adjustment included log10 CRP, log10 hANP, and Kt/V. P-index models used the primary covariates listed in Table 3. Effect-difference P values are marker-by-exposure interactions. CI, confidence interval; Delta (Δ), 3-month change.

Temporal and sensitivity analyses

Each 1-mg/dL higher prior mean phosphorus predicted 1.10 more subsequent P-index points after adjustment (95% CI 0.72–1.49; P < 0.001; 415 transitions). Prior mean P-index did not clearly predict next-quarter BChE (0.35% per 6 points; 95% CI -0.02 to 0.72%; P = 0.067; 438 complete-case transitions from 110 participants). Baseline-adjusted, alternative-calcium, restricted, outlier, inflammation, tenapanor, and leave-one-patient-out analyses supported the contemporaneous primary estimate (Fig. 2; Additiona file 1: Table S1).

Exploratory sex-stratified estimates were positive but imprecise in women. Phosphorus/P-index composite measures were associated with BChE change, but the centered interaction was not (P = 0.455), providing no evidence of synergy beyond the component measures.

Discussion

Principal findings

The principal finding was a contemporaneous within-patient association between post-laboratory prescribed P-index and BChE change after adjustment for measured covariates. Sustained nPCR and BChE co-tracked before adjustment for volume and dialysis dose, whereas prior P-index did not clearly predict next-quarter BChE. These results identify an association for further study but do not validate BChE as a marker of protein intake or establish clinical utility.

Interpretation

The nPCR findings require caution. Their attenuation after hANP and Kt/V adjustment may reflect fluid-related or systemic deterioration affecting both nPCR and BChE, while Kt/V and nPCR share urea-kinetic inputs. Thus, the unadjusted association indicates longitudinal co-tracking rather than an intake-specific response.

Phosphorus connected nPCR with prescribing. The strong nPCR-phosphorus association is compatible with shared dietary exposure, although food source, additives, absorption, dialysis removal, and mineral metabolism make phosphorus an imperfect intake marker [7–10]. Prior phosphorus predicted subsequent P-index escalation, consistent with P-index recording a clinician-mediated response to serial phosphorus measurements.

Interpretation of the P-index-BChE association

The P-index was designed to represent prescribed intensity beyond tablet count. Its relative weights were informed by published equivalent-dose and Japanese comparative data [16–22], but do not establish pharmacologic equivalence. Tenapanor was treated by observed phosphorus-lowering effect rather than binding capacity.

The primary association is contextual rather than pharmacologic. Because the P-index represented the regimen prescribed after review of the corresponding laboratory results, medication intensification did not precede BChE measurement. The result therefore links the BChE trajectory with the clinician's response to phosphorus patterns; it cannot show that medication caused BChE change. Decisions also reflected calcium, PTH, symptoms, tolerance, pill burden, adherence, and intensified dietary counseling. Neither BChE nor nPCR guided prescriptions, reducing direct circularity but not time-varying clinician-mediated confounding. The inconclusive lagged result further supports interpreting P-index only as a study-specific record of prescribed phosphorus-management intensity. Nutritional status, phosphorus,

BChE and prescribing may also change together through unmeasured common causes; no temporal direction can be established from this association.

Comparison with albumin and additional analyses

nPCR tracked both BChE and albumin before core adjustment, and their adjusted associations did not differ. Conversely, P-index change was more strongly associated with BChE. This difference indicates that the associations with prescribed intensity differed between the two biomarkers; it does not establish superiority of BChE or demonstrate that either marker measures dietary intake.

Mineral-bone analyses primarily addressed confounding. Alternative calcium specifications supported the primary estimate, but albumin-adjusted calcium is an imperfect surrogate for ionized calcium in kidney failure [23]. Total ALP could not be assigned specifically to bone turnover because bone-specific ALP was unavailable [24]. These exploratory analyses were not multiplicity-adjusted.

Strengths and limitations

Strengths include standardized monthly measurements, explicit prescription timing, fixed-effects models, patient-clustered inference, stable dialysis frequency, and consistent sensitivity estimates.

Limitations include the single-center retrospective design, selection of a stable prevalent cohort, absence of direct dietary assessment, appetite measures, validated nutrition scores, handgrip strength, and body composition, and lack of external validation. P-index is an unvalidated semiquantitative measure of prescribed intensity, not dietary intake, adherence, or exact phosphate-lowering potency. Prescribing and dietary counseling were not fully protocolized, and adherence was not objectively measured. Residual kidney function, urine output, vitamin D receptor activators, and calcimimetics were not modeled. Liver cirrhosis was excluded, but subclinical hepatic disease, inflammation, medication, and genetic variation may affect BChE. Multiple analyses were exploratory and not preregistered, and residual confounding remains. In the absence of direct dietary intake, body composition, or functional assessments, the observed association cannot determine whether BChE reflects nutrition, phosphorus exposure, or prescribing. Clinical usefulness was not tested.

Conclusions

Within-patient changes in the study-specific prescribed phosphate-lowering intensity score and BChE were associated over the same interval, while the lagged estimate was inconclusive. These exploratory findings describe co-occurring changes and do not validate the score as a measure of dietary intake or demonstrate a clinical application.

Abbreviations

ALP
alkaline phosphatase

BChE
butyrylcholinesterase
CI
confidence interval
CRP
C-reactive protein
GNRI
geriatric nutritional risk index
hANP
human atrial natriuretic peptide
HDF
hemodiafiltration
nPCR
normalized protein catabolic rate
PTH
parathyroid hormone.

Declarations

Ethics approval and consent to participate:

All procedures involving human participants were performed in accordance with the ethical standards of the institutional research committee and the 1964 Declaration of Helsinki and its later amendments. The study was approved by the Ethics Committee of Uji Tokushukai Medical Center, Japan (approval No. 2026-34).

Informed consent:

The requirement for written informed consent was waived because of the retrospective observational design and use of routinely collected clinical data. Patients were provided an opportunity to opt out in accordance with institutional policy.

Consent for publication:

Not applicable.

Competing interests:

The authors declare that no conflict of interest exists.

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Availability of data and materials: Deidentified participant-level data are not publicly available because of institutional and ethical restrictions. Deidentified data and analytic code may be available from the corresponding author upon reasonable request and subject to institutional and ethics committee approval.

Author Contribution

H.N. : Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing - original draft, Writing - review and editing. R.K. : Investigation, Validation, Writing - review and editing.

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Figures

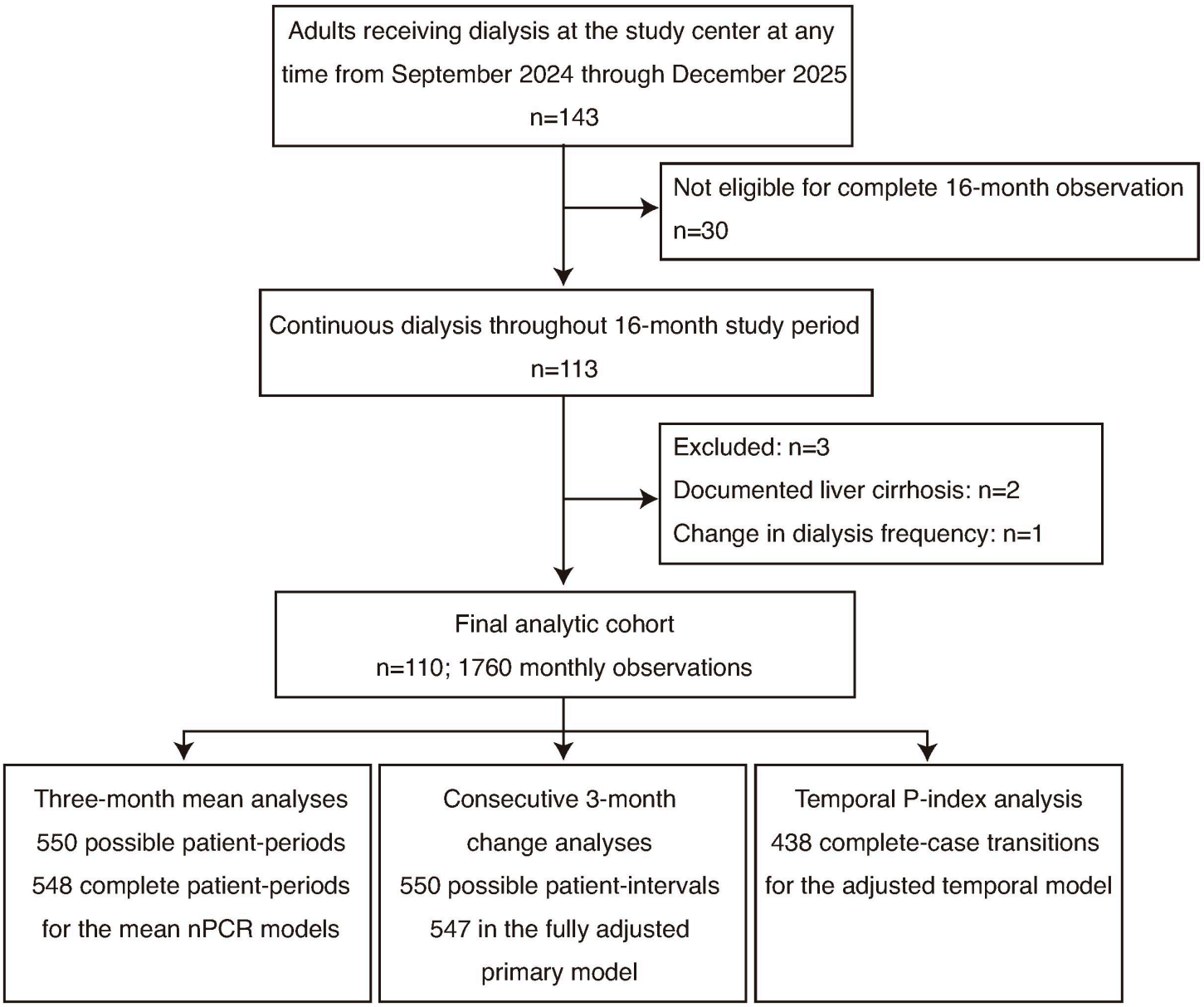


Figure 1

Participant selection and longitudinal analysis datasets

Flow diagram of participant selection and longitudinal datasets. Five 3-month mean periods yielded 550 possible patient-periods (548 complete for mean nPCR models). Five consecutive 3-month changes yielded 550 possible intervals (547 in the primary model). The lagged analysis included 438 complete-case transitions from 110 participants.

BChE, butyrylcholinesterase; nPCR, normalized protein catabolic rate; P-index, prescribed phosphate-lowering medication intensity index.

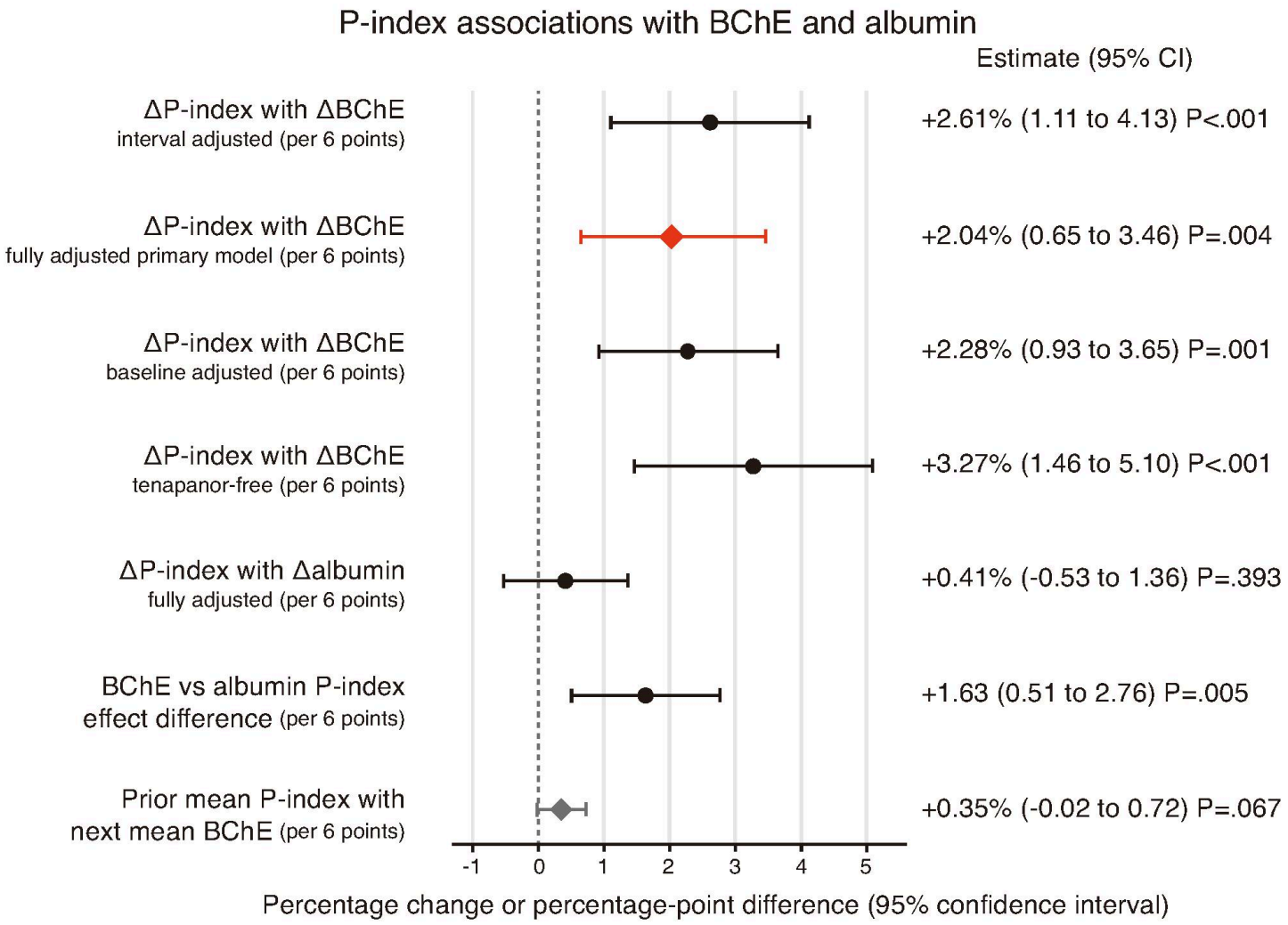


Figure 2

Forest plot of key longitudinal associations

Points and bars show estimates and 95% confidence intervals. The red diamond identifies the primary analysis; the gray diamond identifies the lagged analysis. Adjusted P-index models included sex and concurrent changes in nPCR, phosphorus, log10 CRP, log10 hANP, Kt/V, total calcium, log10 PTH, and log10 total ALP. P-index reflected prescriptions issued after review of the corresponding laboratory results; same-interval associations do not imply temporal precedence or a medication effect. The BChE-versus-albumin row is the marker-by-P-index interaction (P = 0.005).

BChE, butyrylcholinesterase; CI, confidence interval; CRP, C-reactive protein; hANP, human atrial natriuretic peptide; nPCR, normalized protein catabolic rate; P-index, prescribed phosphate-lowering medication intensity index; PTH, parathyroid hormone.

Supplementary Files

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