

Serum Phosphorus, Not Calcium, Underlies the Rising Calcium–Phosphorus Ratio in More Severe Essential Hypertension: A Robustness-Tested Cross-Sectional Study

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Abstract

Background.

Calcium and phosphorus homeostasis influences vascular tone and blood-pressure regulation, yet the integrated calcium–phosphorus (Ca/P) ratio is seldom studied in essential hypertension, and prior reports rarely exclude renal or endocrine confounders or relate minerals to formally graded severity. We evaluated serum calcium, phosphorus and the Ca/P ratio and their association with hypertension severity and electrocardiographic target-organ damage.

Methods.

In this cross-sectional study at a tertiary centre in Chengalpattu, 171 adults with primary hypertension—after excluding renal, endocrine, secondary-hypertensive, hepatic, pregnant and supplement-using patients—underwent measurement of total calcium (colorimetric), phosphorus, and the calculated Ca/P ratio and Ca×P product. Blood pressure was graded by the ESH 2023 guideline and target-organ damage by electrocardiography. Analyses used non-parametric tests, multi-method correlation and multivariable ordinal regression, with pre-specified robustness analyses (isometric log-ratio modelling, distance correlation, E-values, specification-curve analysis and penalised regression).

Results.

Mean calcium was 8.88 ± 0.69 and phosphorus 3.11 ± 0.56 mg/dL; hypocalcaemia occurred in 15.2%. From grade 1 to grade 3, phosphorus fell and the Ca/P ratio rose monotonically (Jonckheere trend $p < 0.001$ and $p = 0.0005$), while calcium showed only a borderline, non-significant decline (trend $p = 0.050$). The Ca/P ratio correlated positively, and phosphorus negatively, with blood pressure ($|p| 0.20$ – 0.28). After adjustment, each unit of Ca/P more than doubled the odds of higher grade (OR 2.50, 95% CI 1.35–4.63, $p = 0.003$); compositional modelling pointed to overall mineral magnitude—driven by phosphorus—rather than the calcium-to-phosphorus balance, although the two coordinates were collinear and could not be cleanly separated. The effect was significant in 88% of 32 specifications (E-value ≈ 1.7). No mineral discriminated electrocardiographic left ventricular hypertrophy (AUC 0.53–0.57).

Conclusions.

The Ca/P ratio rises with hypertension severity, driven by declining phosphorus rather than rising calcium; total calcium was neither depressed nor severity-related, and minerals did not predict left ventricular hypertrophy. This robust but modest association warrants confirmation using ionised calcium and echocardiography.

Background

Hypertension is the single largest modifiable contributor to cardiovascular disease and premature death worldwide, and its burden continues to grow: the number of adults aged 30–79 years living with hypertension doubled between 1990 and 2019 to an estimated 1.28 billion, even as age-standardised prevalence remained broadly stable [1]. The burden is particularly heavy in India, where the nationally representative ICMR-INDIAB survey reported a hypertension prevalence of 35.5%, with a large proportion of cases undiagnosed or inadequately controlled [2]. Because blood-pressure control remains suboptimal despite the availability of effective therapy, there is sustained interest in modifiable biochemical correlates of hypertension that may illuminate its pathophysiology or assist risk stratification.

Calcium has long been implicated in blood-pressure regulation through its central role in vascular smooth-muscle physiology. Vascular tone reflects the contractile state of smooth-muscle cells, which depends on intracellular free calcium driving actin–myosin cross-bridge formation, modulated additionally by calcium-independent RhoA/Rho-kinase and oxidant signalling [3]. The membrane potential established by the interplay of voltage-dependent calcium channels and potassium channels governs calcium entry and thus the degree of contraction, and altered expression or function of these channels has been linked to essential hypertension [4]. These mechanisms provide a biologically plausible basis for a relationship between systemic calcium status and blood pressure, underpinning the long-standing clinical interest in serum calcium as a marker of hypertensive disease.

Empirically, however, studies of serum calcium in essential hypertension have yielded conflicting results: some report lower calcium in hypertensive than normotensive individuals with an inverse calcium–pressure relationship [5], whereas others observe higher systolic pressure at higher corrected-calcium concentrations [6]. Calcium does not act in isolation; it is co-regulated with phosphorus, and disturbances of both minerals are associated with vascular calcification and cardiovascular mortality, with lower calcium and higher phosphorus each predicting adverse outcomes in coronary and dialysis populations [7–9]. This co-regulation has prompted interest in the calcium–phosphorus (Ca/P) ratio and the $\text{Ca} \times \text{P}$ product as integrated indices of mineral status. Yet the available evidence is dominated by chronic kidney disease and established cardiovascular disease, in which mineral derangement is driven largely by renal failure; the Ca/P ratio has seldom been examined in essential hypertension free of renal and endocrine disease, and almost never related to formally graded disease severity. Whether mineral status tracks the severity of hypertension itself, independent of these confounders, therefore remains unclear.

We undertook this cross-sectional study to address that gap. In patients with essential hypertension—rigorously excluding renal, endocrine and secondary causes—we estimated serum total calcium, serum phosphorus and the Ca/P ratio; correlated these parameters with hypertension severity graded by the European Society of Hypertension 2023 and Indian Hypertension Guidelines; and assessed their association with hypertension-mediated target-organ damage on electrocardiography. The principal

findings were then subjected to a series of robustness analyses to determine whether any mineral–severity association was genuine rather than an artefact of analytical choices.

Methods

Study design and setting. This observational cross-sectional study was conducted in the Department of General Medicine of Shri Sathya Sai Medical College and Research Institute, Ammapettai, Chengalpattu district, Tamil Nadu—a tertiary-care teaching hospital—over an 18-month period. Consecutive eligible patients attending the outpatient and inpatient services were enrolled after the purpose and procedures of the study had been explained and written informed consent obtained.

Participants. Adults aged 18 years or older, of either sex, with a diagnosis of primary (essential) hypertension were eligible. To isolate mineral changes attributable to hypertension itself rather than to comorbid disease, we applied stringent exclusions for conditions known to perturb calcium–phosphorus homeostasis or to cause secondary hypertension: current vitamin D or calcium supplementation; renal parenchymal or vascular disease; endocrine disorders including thyroid or parathyroid dysfunction and diabetes mellitus; pheochromocytoma or primary aldosteronism; chronic liver disease; and pregnancy. Eligibility was determined by history, clinical examination and available investigations. Each participant underwent detailed history-taking covering demographic characteristics, lifestyle habits and cardiovascular risk factors, followed by a complete physical and systemic examination.

Sample size. The sample size was calculated from a previous study reporting a 52.4% prevalence of low serum calcium in stage 1 hypertension, using the standard formula for estimating a single proportion at 95% confidence and 8% absolute precision (margin of error $d = 8\%$). After adding 10% for potential non-response, the required size was 171 participants. The prevalence of hypocalcaemia observed in the present cohort (15.2%) differed appreciably from this prior estimate, a discrepancy considered when interpreting the findings.

Measurements. After standardised phlebotomy under aseptic precautions, serum total calcium was measured by an established colorimetric method and serum inorganic phosphorus by a routine biochemical assay; the Ca/P ratio was derived as calcium divided by phosphorus and the $\text{Ca} \times \text{P}$ product as their multiple. Hypocalcaemia (serum calcium < 8.5 mg/dL), hypophosphataemia (< 2.5 mg/dL) and hyperphosphataemia (> 4.5 mg/dL) were defined by laboratory reference limits (normal ranges: calcium 8.5–10.5 and phosphorus 2.5–4.5 mg/dL), and the Ca/P ratio was banded as low (< 2.3), normal (2.3–2.7) or high (> 2.7). Blood pressure was recorded with a calibrated sphygmomanometer in a standardised manner; two readings were obtained and averaged for all analyses. Severity was classified as grade 1–3 hypertension following the European Society of Hypertension (ESH) 2023 guideline and cross-checked against the Indian Hypertension Guidelines II, which yielded concordant grading. Body mass index was calculated and categorised using Asian-Indian thresholds. A 12-lead electrocardiogram was recorded in every participant and interpreted for left ventricular hypertrophy (LVH) and ST–T changes; hypertension-mediated target-organ damage was operationalised as electrocardiographic LVH.

Statistical analysis. Data were entered in a structured proforma and analysed using SPSS v23 and R version 4.6.0. Distributional normality was assessed by the Shapiro–Wilk and Anderson–Darling tests; because most variables departed from normality, non-parametric methods were used throughout. Continuous variables are summarised as mean $\pm$ SD and median[IQR], and categorical variables as frequency (%) with 95% Wilson confidence intervals. Differences in mineral parameters across the three hypertension grades were examined by the Kruskal–Wallis test, with the Jonckheere–Terpstra test for ordered trend and Dunn pairwise comparisons adjusted by the Benjamini–Hochberg procedure. Associations of minerals with blood-pressure indices were quantified by Spearman correlation, by partial correlation adjusted for age, sex and BMI, and by distance correlation to detect non-linear dependence. The primary multivariable model was an ordinal (proportional-odds) logistic regression of hypertension grade. Discrimination of severity and target-organ damage was assessed by receiver-operating-characteristic (ROC) analysis. A two-sided $p < 0.05$ was considered significant.

Robustness analyses. Several pre-specified sensitivity analyses examined the stability of the severity association. Because the Ca/P ratio is compositional, the calcium–phosphorus pair was re-expressed as isometric log-ratio (ilr) balance and size coordinates and re-modelled, with variance-inflation factors compared against the raw parameterisation. Ordinal association between mineral categories and grade was summarised using Goodman–Kruskal gamma, Somers' D and Kendall τ -b. E-values quantified robustness to unmeasured confounding. A specification-curve analysis re-estimated the effect across 32 specifications formed by two co-directional exposures (the raw Ca/P ratio and the isometric log-ratio balance) crossed with eight covariate sets and two outcome codings. A Mahalanobis distance summarised joint mineral atypicality, principal component analysis described the multivariate structure, and penalised (elastic-net) and Firth logistic regression guarded against overfitting in the LVH models.

Ethics. The study was approved by the Institutional Human Ethics Committee of Shri Sathya Sai Medical College and Research Institute (approval no. IEC 1110/25; committee registration no. ECR/1871/Inst/TN/2023), on 17 February 2025. All participants provided written informed consent, confidentiality of data was maintained, and investigations were performed solely for the purpose of this study.

Results

Cohort characteristics. The 171 participants (Fig 1; Table 1) had a mean age of 52.7 years and were predominantly male (60.2%) and overweight or obese by Asian-Indian criteria (76.0%). Mean office blood pressure was 160.6/101.0 mmHg, distributed across ESH grade 1 (40.4%), grade 2 (36.8%) and grade 3 (22.2%), with one high-normal patient. The electrocardiogram was abnormal in 57.3%, comprising LVH in 36.8% and ST–T changes in 20.5%, and half the cohort reported a family history of hypertension. The two within-visit blood-pressure readings agreed well for systolic pressure (intraclass correlation 0.74; Supplementary Table S1), supporting their averaging.

Fig 1. Study flow diagram. Consecutive adults with primary essential hypertension were enrolled after pre-specified exclusions for conditions perturbing calcium–phosphorus homeostasis or causing secondary hypertension. All 171 enrolled participants underwent serum mineral measurement, ESH 2023 blood-pressure grading and 12-lead electrocardiography. The severity analysis was restricted to the 170 grade 1–3 patients (one high-normal excluded); descriptive, correlation and target-organ-damage analyses used the full cohort (n = 171).

Serum mineral levels (Objective 1). Mean serum calcium (8.88 mg/dL) and phosphorus (3.11 mg/dL) both lay in the lower-normal range, with full distributions in Table 1. Hypocalcaemia was present in 15.2%, hypophosphataemia in 16.4% and hyperphosphataemia in 8.8%, and the Ca/P ratio fell in the predefined "high" band in 62.0% of patients—indicating that, despite generally preserved calcium, the ratio exceeded the conventional upper limit (>2.7) in a majority even though only 16.4% of patients were frankly hypophosphataemic, reflecting that this reference band—derived for higher phosphorus concentrations—classifies a largely normophosphataemic cohort as high and should be interpreted with caution here.

Minerals and hypertension severity (Objective 2). Mineral concentrations diverged systematically with severity (Fig 2; Table 2, Panel A). Serum phosphorus and the Ca×P product declined progressively from grade 1 to grade 3, while the Ca/P ratio rose; all three differed significantly across grades and showed concordant ordered trends (Jonckheere trend $p < 0.001$ for each), whereas serum calcium showed only a shallow, borderline decline that met neither the omnibus test (Kruskal–Wallis $p = 0.102$) nor, at our pre-specified $p < 0.05$ threshold, the ordered-trend test (Jonckheere $p = 0.050$). Dunn comparisons localised the gradient chiefly to the grade 1 versus grade 3 contrast. The decisive observation is that the rise in the ratio was produced by falling phosphorus, not by rising calcium.

Fig 2. Serum minerals across hypertension severity. Box-and-whisker plots of (A) serum calcium, (B) serum phosphorus, (C) the Ca/P ratio and (D) the Ca×P product across ESH 2023 grades (n = 170). Boxes show median and interquartile range, whiskers the $1.5 \times \text{IQR}$, white diamonds the mean. Serum phosphorus and the Ca×P product fell, and the Ca/P ratio rose, monotonically from grade 1 to 3 (Jonckheere–Terpstra trend $p < 0.001$, 0.0002 and 0.0005); calcium showed only a borderline, non-significant decline ($p = 0.050$).

The continuous correlations reproduced this pattern (Fig 3; Table 2, Panel B). Phosphorus and the Ca×P product correlated negatively, and the Ca/P ratio positively, with systolic, diastolic and mean arterial pressure, calcium showing weaker negative coefficients; the strongest single association was the Ca×P product with mean arterial pressure. All magnitudes were nonetheless modest ($|p|$ 0.17–0.28). These coefficients were essentially unchanged after adjustment for age, sex and BMI, and distance correlation—sensitive to non-linear as well as linear dependence—was of similar or slightly greater magnitude, indicating the relationship was genuine and not an artefact of linear modelling. Among categorical measures (Table 2, Panel C), phosphorus category showed a clear ordinal association with grade (gamma -0.48), whereas calcium and Ca/P categories did not.

Fig 3. Relationships between serum minerals and blood pressure. (A) Spearman correlation matrix of continuous variables (n = 171). (B–D) Scatter plots with linear fit and 95% confidence band for average systolic blood pressure versus (B) serum phosphorus, (C) the Ca/P ratio and (D) the Ca×P product. Phosphorus and the Ca×P product correlated negatively, and the Ca/P ratio positively, with blood pressure (all Benjamini–Hochberg-adjusted $p < 0.05$).

Mineral levels did not differ by sex, diet, smoking, alcohol, tobacco or betel-nut use, or BMI category (Supplementary Table S2), confirming that the severity gradient was not a proxy for lifestyle or anthropometry. The principal exceptions were a slightly lower calcium in patients with pallor and modestly higher minerals in those with an abnormal electrocardiogram; the latter runs counter to the grade gradient and most plausibly reflects the heterogeneous drivers of the pooled electrocardiographic-abnormality category rather than a true mineral effect.

In multivariable analysis (Fig 4A; Table 3, Panel A), serum phosphorus was the only mineral independently predicting higher grade in the model containing both calcium and phosphorus (OR 0.50 per mg/dL, $p=0.011$); in the collinearity-safe model, each unit increase in the Ca/P ratio more than doubled the odds of a higher grade (OR 2.50, 95% CI 1.35–4.63, $p=0.003$), with age, sex and BMI non-contributory. Recasting the mineral pair into compositional coordinates indicated that the severity signal was carried by the overall mineral-magnitude (size) coordinate (OR 0.037, $p=0.016$), whereas the calcium-to-phosphorus balance coordinate was non-significant but imprecisely estimated (OR 1.831, 95% CI 0.084–40.08) because the two coordinates are correlated; these results are consistent with, but cannot isolate, phosphorus as the active component.

Fig 4. Multivariable model and robustness analyses. (A) Adjusted odds ratios (95% CI) from ordinal proportional-odds regression of blood-pressure grade; † denotes the Ca/P ratio from the collinearity-safe model. (B) Specification-curve analysis across 32 specifications (dotted line, median estimate). (C) E-values for the principal mineral–severity associations (filled, point estimate; open, 95% CI bound). (D) Distance correlation versus absolute Pearson and Spearman coefficients with systolic blood pressure.

These findings were stable under pre-specified stress-testing (Fig 4B–D; Table 3, Panel B). The compositional reparameterisation roughly halved collinearity (variance inflation 4.4→1.75). Across 32 model specifications the effect retained the same direction in 100% and reached significance in 88%. E-values were approximately 1.7, implying that an unmeasured confounder would need a moderate association with both exposure and outcome to explain the result away. A multivariate Mahalanobis distance summarising joint mineral atypicality increased significantly across grades, and the first principal component—a pressure-versus-mineral contrast accounting for 29% of variance—separated grades strongly (S1 Fig).

Minerals and target-organ damage (Objective 3). In contrast to the severity findings, no mineral discriminated electrocardiographic LVH (Fig 5; Table 3, Panel C). Areas under the ROC curve ranged from 0.53 to 0.57, none better than chance, and DeLong comparisons showed no biomarker superior to another. For discrimination of grade ≥ 2 , phosphorus performed best though still only fairly (AUC 0.65).

Penalised (elastic-net) regression shrank every candidate mineral predictor of LVH to zero, and Firth regression confirmed that only older age, not mineral status, was associated with LVH. Although electrocardiographic abnormality itself increased with hypertension grade (Supplementary Table S2), this tracked severity rather than mineral derangement, and supplementary unadjusted and linear analyses (Supplementary Table S3) were concordant with the models above.

Fig 5. Serum minerals and electrocardiographic target-organ damage. ROC curves for discrimination of (A) grade ≥ 2 hypertension and (B) electrocardiographic LVH (AUC in legend; in-sample estimates). (C) Distribution of ECG categories across blood-pressure grade (Cochran–Armitage trend $p < 0.001$). (D) Adjusted odds ratios (95% CI) for LVH from Firth penalized logistic regression; only older age was associated with LVH.

Discussion

This study examined serum calcium, phosphorus and the calcium–phosphorus (Ca/P) ratio across the severity spectrum of essential hypertension in a cohort rigorously screened to exclude renal, endocrine and secondary causes. Four observations emerge: serum calcium was neither depressed nor related to severity; serum phosphorus fell and the Ca/P ratio rose monotonically with grade, the ratio being driven by declining phosphorus and the severity signal residing in overall mineral magnitude rather than the calcium-to-phosphorus balance; mineral status correlated only modestly with blood pressure; and no mineral predicted electrocardiographic left ventricular hypertrophy (LVH). Each is considered against the literature below.

Serum calcium and severity. Our near-flat calcium gradient and lower-normal mean concentration both contrast with and help reconcile a conflicting literature. Some case–control studies report lower calcium in hypertensive than normotensive individuals with an inverse calcium–pressure relationship [5], others find higher systolic pressure at higher corrected-calcium concentrations [6], and lower calcium has been linked to greater cardiovascular mortality in coronary disease [7]. Our data align with neither extreme: within an already established hypertensive cohort, total calcium did not track severity. The hypocalcaemia prevalence of 15.2% was far below the 52.4% reported in the stage 1 hypertensive population on which our sample size was based, and far below the roughly 61% seen in chronic kidney disease (CKD), where mineral disturbance is driven by renal failure [10]. This implies that, once overt renal and endocrine disease is excluded, frank calcium deficiency is uncommon and total calcium is a poor severity marker. The interpretation is tempered by our use of total rather than ionised or albumin-corrected calcium; notably, calcium is not biologically inert in the vasculature, as higher calcium concentrations can worsen large-artery stiffness [11], so a true ionised-calcium signal may have been masked.

Serum phosphorus as the active component. The most consistent biochemical signal was a progressive fall in phosphorus with rising grade, mirrored by negative phosphorus–pressure correlations and a significant ordinal regression coefficient. This direction is opposite to the canonical CKD–mineral and

bone disorder (CKD-MBD) pattern, in which impaired renal excretion drives phosphate upward—hyperphosphataemia reaching ~ 82% prevalence and worsening with stage [10]—with elevated phosphate predicting vascular calcification and cardiovascular death in renal and coronary populations [7, 8, 9, 12]. The contrast is sharpened by experimental work: chronic excess dietary phosphate raises arterial pressure in mice by activating the renin–angiotensin–aldosterone system and sympathetic tone, independent of PTH [13]. That both higher dietary phosphate (experimentally) and lower serum phosphorus (in our cohort) accompany higher pressure is only superficially paradoxical—dietary phosphate loading and steady-state serum phosphorus are distinct, and in established hypertension increased phosphaturia could lower circulating phosphorus even as pressure rises. Reassuringly, phosphate appears to have little direct effect on large-artery stiffness [11], consistent with any phosphorus–pressure link being hormonally rather than structurally mediated. Although population data relating serum phosphate to blood pressure remain limited and inconsistent, our findings indicate that, absent renal failure, lower serum phosphorus accompanies more severe hypertension—most plausibly reflecting altered phosphaturic hormonal activity rather than dietary intake or impaired excretion.

The Ca/P ratio and a compositional caution. Because phosphorus fell while calcium changed little, the Ca/P ratio rose with severity, and in adjusted analysis each unit increment more than doubled the odds of higher grade. The ratio is attractive precisely because it compresses two co-regulated minerals into a single, inexpensive, laboratory-derived index, and it has demonstrated practical value elsewhere: the serum Ca/P ratio discriminates primary hyperparathyroidism with high sensitivity and specificity at a cut-off near 3.35 mg/dL [14], and the reciprocal phosphorus-to-calcium ratio independently predicts mortality in acute pancreatitis [15]. Its application to grading essential hypertension, however, is novel. Crucially, our compositional (isometric log-ratio) analysis attributes the severity signal to overall mineral magnitude—driven by phosphorus—rather than to the calcium-to-phosphorus balance, although the balance and magnitude coordinates are collinear and cannot be fully separated. The apparent predictive value of the ratio is therefore, mechanistically, a phosphorus effect in disguise; reporting the ratio without this decomposition would have overstated the contribution of calcium and risked the well-recognised fallacy of attributing meaning to a ratio whose denominator carries the signal. The ratio may still serve as a convenient composite, but its interpretation should remain anchored to phosphorus.

Correlation structure, subgroups and an internal tension. The mineral–pressure associations were modest in magnitude (correlation coefficients 0.17–0.28) yet internally consistent: Spearman, age/sex/BMI-adjusted partial, and distance correlations agreed in direction and significance, and the distance correlation—sensitive to non-linear dependence—was of similar or slightly greater magnitude, arguing against a purely linear artefact. Modest effect sizes are themselves concordant with a literature in which mineral–blood-pressure relationships are generally weak and inconsistent [5, 6], and they reinforce that any clinical value lies at the population rather than the individual level. Mineral concentrations did not differ by sex, diet, smoking, alcohol, tobacco use or body-mass category, indicating that the severity gradient is not a proxy for lifestyle or adiposity. One finding requires explicit comment: minerals were paradoxically higher, not lower, in patients with an abnormal electrocardiogram, opposite to the grade gradient. This most plausibly reflects confounding within a heterogeneous, pooled

"ECG-abnormal" category that combines LVH with ST–T changes of ischaemic and other origin, rather than a true reversal of the mineral–severity relationship, and it underscores why the formal severity analyses—rather than this composite electrocardiographic flag—carry the principal message.

Minerals and left ventricular hypertrophy. No mineral discriminated electrocardiographic LVH, and penalised regression shrank every mineral predictor to zero, even though electrocardiographic abnormality itself rose with grade—the expected relationship between blood-pressure severity and hypertension-mediated organ damage. This null accords with current mechanistic understanding: the principal mineral-related driver of myocardial hypertrophy is neither serum calcium nor phosphorus but fibroblast growth factor 23 (FGF23), which directly induces cardiomyocyte hypertrophy and is strongly associated with LVH [16], and which, with PTH, links mineral metabolism to cardiac remodelling in CKD-MBD [12]. Even experimentally, elevated phosphate does not invariably produce hypertrophy: phosphate-loaded mice developed higher blood pressure without LVH [13], mirroring our own dissociation between the mineral–severity and mineral–LVH findings. Because FGF23 was not—and in routine practice could not be—measured, a null association between static serum minerals and LVH is unsurprising. The finding is further constrained by reliance on electrocardiography, which is insensitive for left-ventricular mass relative to echocardiography; the absence of association therefore applies specifically to electrocardiographic LVH.

Possible mechanisms. The associations are most plausibly mediated by the mineral-regulating hormonal axis we could not measure. PTH is independently related to central blood pressure, wave reflection and systemic vascular resistance even in subjects free of cardiovascular comorbidity [17]; consistent with this, PTH appears to act on resistance vessels and wave reflection rather than large-artery stiffness [11], and parathyroid disorders cluster with hypertension and the metabolic syndrome [18]. Vitamin D, which governs calcium and phosphate handling, has been causally linked to blood pressure in Mendelian randomisation, higher 25-hydroxyvitamin D predicting lower pressure and reduced hypertension risk [19]. FGF23 and PTH jointly regulate phosphate excretion and are activated before overt mineral change occurs [12], and excess phosphate can raise pressure through the renin–angiotensin–aldosterone system and sympathetic activation [13]. A coherent synthesis is that subclinical up-regulation of phosphaturic and calcaemic hormones in more severe hypertension lowers serum phosphorus while defending calcium, generating the observed gradients and operating through the vascular-tone pathways—including intracellular calcium handling in vascular smooth muscle—that govern blood pressure [3]. This remains hypothesis: our cross-sectional design cannot establish direction or causation.

Strengths. The principal strength is the cohort: by excluding renal, endocrine and secondary disease, we isolated mineral changes attributable to essential hypertension, distinguishing this work from the CKD- and cardiovascular-disease-dominated literature that shapes current understanding [10, 12]. Methodologically, the severity association withstood compositional reanalysis, distance correlation, a 32-specification curve and E-value assessment. Multiverse/specification-curve analysis quantifies how an estimate behaves across all defensible analytical choices and guards against selective reporting [20],

while the E-value of ~ 1.7 indicates that a moderate unmeasured confounder would be required to nullify the association [21]. Such layered robustness testing is rarely applied in this field and strengthens confidence that the association is genuine rather than an artefact of analytic flexibility.

Limitations. Several limitations temper these conclusions. The cross-sectional design precludes causal or temporal inference, and the single-centre, hospital-based setting limits generalisability to community populations. Antihypertensive treatment status was not recorded, so office blood pressure and ESH grade may reflect treated rather than untreated pressure, leaving the severity gradient potentially confounded by therapy. We measured total rather than ionised or albumin-corrected calcium. Critically, we did not measure PTH, vitamin D, FGF23 or renal function—the very mediators implicated above [12, 16, 17, 19]—whose absence is the chief residual confounder and is consistent with the modest E-values. LVH was assessed electrocardiographically rather than echocardiographically, and the mineral–severity effect sizes were modest, so the Ca/P ratio is best regarded as a population-level correlate rather than an individual diagnostic test. Clinically, these data argue against using total serum calcium to gauge hypertension severity and indicate that any mineral contribution is better captured by phosphorus or the Ca/P ratio. Prospective, multicentre studies incorporating ionised calcium, the phosphaturic hormonal axis, renal function, echocardiography and a normotensive comparator are required to confirm and explain these findings.

Conclusions

In this renal- and endocrine-free cohort of patients with essential hypertension, the calcium–phosphorus ratio rose monotonically with disease severity, but this gradient was driven by a progressive fall in serum phosphorus rather than any rise in calcium. Total serum calcium was neither depressed nor related to severity, and the ratio's association with grade survived multivariable adjustment, compositional reanalysis, testing across 32 specifications and evaluation of unmeasured confounding. No mineral parameter predicted electrocardiographic left ventricular hypertrophy by any method, with only age remaining associated. The calcium–phosphorus ratio may therefore serve as a simple, inexpensive correlate of hypertension severity, but its effect size is modest and its mechanism—plausibly involving the unmeasured parathyroid hormone–vitamin D–FGF23 axis—remains undefined. Because the study was cross-sectional and single-centre and relied on total rather than ionised calcium and on electrocardiographic rather than echocardiographic assessment of hypertrophy, these associations are best regarded as robust but hypothesis-generating. Confirmation in prospective, multicentre cohorts incorporating ionised or albumin-corrected calcium, mineral-regulating hormones, renal-function measures, echocardiography and a normotensive comparison group is required before any clinical application can be considered.

Abbreviations

Ca/P
calcium–phosphorus ratio

Ca×P
calcium–phosphorus product
BP
blood pressure
SBP
systolic blood pressure
DBP
diastolic blood pressure
MAP
mean arterial pressure
PP
pulse pressure
ESH
European Society of Hypertension
LVH
left ventricular hypertrophy
ECG
electrocardiography
BMI
body mass index
SD
standard deviation
IQR
interquartile range
OR
odds ratio
CI
confidence interval
ROC
receiver-operating-characteristic
AUC
area under the curve
ilr
isometric log-ratio
CKD
chronic kidney disease
PTH
parathyroid hormone
FGF23
fibroblast growth factor 23

Declarations

Ethics approval and consent to participate:

This study was approved by the Institutional Human Ethics Committee of Shri Sathya Sai Medical College and Research Institute (IEC No. 1110/25; committee registration no. ECR/1871/Inst/TN/2023; approved 17 February 2025). All methods and procedures involving human participants were carried out in accordance with the relevant guidelines and regulations, and in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrolment.

Consent for publication:

Not applicable.

Competing interests:

The authors declare that they have no competing interests.

Penalised LVH models

elastic-net regression shrank all mineral predictors to zero; Firth regression — Ca/P ratio OR 1.57 (0.82–3.13), $p = 0.178$; age OR 1.023 (1.002–1.046), $p = 0.031$; sex and BMI non-significant. DeLong comparisons among LVH AUCs all non-significant ($p > 0.24$).

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Author Contribution

KK, MLSJ and NDC conceived and designed the study. KK, VK and SD performed data acquisition and curation. KK carried out the statistical analysis and interpretation. KK and VK drafted the manuscript. MLSJ and NDC supervised the project and critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Not applicable.

Data Availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Tables

Table 1. Baseline demographic, clinical and biochemical characteristics (n = 171)

(A) Continuous variables

Variable	Mean $\pm$ SD	Median [IQR]
Age (years)	52.75 $\pm$ 15.24	53 [39.5–66]
Weight (kg)	70.42 $\pm$ 11.85	70 [62–78]
Height (cm)	164.16 $\pm$ 8.79	164 [158–170]
BMI (kg/m²)	26.14 $\pm$ 4.20	26.0 [23.4–28.9]
Pulse (bpm)	80.79 $\pm$ 13.88	80 [69–94]
Systolic BP (mmHg)	160.57 $\pm$ 15.29	160 [147–170.5]
Diastolic BP (mmHg)	101.01 $\pm$ 8.35	100 [94–106]
Pulse pressure (mmHg)	59.57 $\pm$ 9.75	58 [52–65.5]
Mean arterial pressure (mmHg)	120.86 $\pm$ 10.15	120.3 [112–127.3]
Serum calcium (mg/dL)	8.88 $\pm$ 0.69	8.91 [8.51–9.35]
Serum phosphorus (mg/dL)	3.11 $\pm$ 0.56	3.10 [2.75–3.45]
Ca/P ratio	2.93 $\pm$ 0.48	2.90 [2.62–3.26]
Ca$\times$P product (mg²/dL²)	27.68 $\pm$ 5.65	27.31 [23.89–30.83]

(B) Categorical variables — n (%)

Variable	Category	n (%)
Sex	Male / Female	103 (60.2) / 68 (39.8)
Age group	<40 / 40–49 / 50–59 / 60–69 / ≥70 y	43 (25.1) / 33 (19.3) / 27 (15.8) / 37 (21.6) / 31 (18.1)
Diet	Non-vegetarian / Vegetarian	121 (70.8) / 50 (29.2)
Smoking	Yes	33 (19.3)
Alcohol	Yes	44 (25.7)
Tobacco/betel-nut	Yes	22 (12.9)
Family history of hypertension	Yes / No / Not known	87 (50.9) / 64 (37.4) / 20 (11.7)
BMI (Asian-Indian)	Normal / Overweight / Obese	41 (24.0) / 25 (14.6) / 105 (61.4)
ESH 2023 BP grade	Grade 1 / 2 / 3 / High-normal	69 (40.4) / 63 (36.8) / 38 (22.2) / 1 (0.6)
ECG	Normal / ST–T changes / LVH	73 (42.7) / 35 (20.5) / 63 (36.8)
Calcium category	Normocalcaemia / Hypocalcaemia	145 (84.8) / 26 (15.2)
Phosphorus category	Normo / Hypo / Hyper-phosphataemia	128 (74.9) / 28 (16.4) / 15 (8.8)
Ca/P category	High / Normal / Low	106 (62.0) / 43 (25.1) / 22 (12.9)
Examination findings	Pallor / Pedal oedema / Abnormal CVS / Basal crepitations / Hepatomegaly / Intention tremor	24 (14.0) / 19 (11.1) / 36 (21.1) / 24 (14.0) / 12 (7.0) / 22 (12.9)

Table 2. Serum minerals across hypertension severity and their association with blood pressure

(A) Mineral parameters by ESH 2023 grade – median [IQR], with trend tests (n = 170)

Mineral	Grade 1	Grade 2	Grade 3	Kruskal–Wallis p	Trend p†	Significant pairs‡
Calcium	8.97 [8.56– 9.43]	8.92 [8.51– 9.45]	8.54 [8.51– 9.05]	0.102	0.050	none
Phosphorus	3.12 [2.98– 3.45]	2.93 [2.76– 3.18]	2.76 [2.45– 3.14]	0.0008	<0.001	1–2 (0.036); 1–3 (0.0007)
Ca/P ratio	2.83 [2.62– 3.16]	3.11 [2.62– 3.27]	3.34 [2.64– 3.49]	0.0032	0.0005	1–3 (0.0022)
Ca×P product	28.68 [26.06– 31.91]	27.31 [23.94– 30.56]	25.14 [20.85– 27.98]	0.0009	0.0002	1–3 (0.0006); 2–3 (0.045)

†Jonckheere–Terpstra ordered-trend test. ‡Dunn pairwise comparisons, Benjamini–Hochberg-adjusted p in parentheses.

(B) Correlation of minerals with blood-pressure indices – Spearman ρ / partial ρ § / distance correlation
(n = 171)

Mineral	vs SBP	vs DBP	vs MAP
Calcium	–0.192 / –0.196 / 0.190	–0.173 / –0.174 / 0.189	–0.184 / –0.195 / 0.194
Phosphorus	–0.261 / –0.267 / 0.297	–0.268 / –0.265 / 0.287	–0.275 / –0.273 / 0.301
Ca/P ratio	+0.204 / +0.210 / 0.280	+0.218 / +0.225 / 0.265	+0.222 / +0.221 / 0.282
Ca×P product	–0.267 / –0.272 / 0.287	–0.271 / –0.273 / 0.295	–0.278 / –0.281 / 0.300

§Partial correlation adjusted for age, sex and BMI. All Spearman coefficients significant at Benjamini–Hochberg $p < 0.05$; all distance correlations significant at permutation $p \leq 0.001$. Distance correlation is reported as a non-negative measure of dependence (linear or non-linear) and is therefore unsigned.

(C) Ordinal association of mineral categories with BP grade (n = 170)

Category	Gamma (95% CI)	Somers' D	Kendall τ -b
Calcium category	–0.145 (–0.467, 0.177)	–0.038	–0.060
Phosphorus category	–0.475 (–0.691, –0.260)	–0.206	–0.262
Ca/P category	+0.145 (–0.082, 0.373)	+0.078	+0.086

Table 3. Multivariable models, robustness analyses, and discrimination of severity and target-organ damage

(A) Ordinal (proportional-odds) regression of hypertension grade (n = 170); odds ratios are expressed per one-unit increase in the predictor

Model / term	OR (95% CI)	p
Model A — Calcium	0.766 (0.506–1.158)	0.206
Phosphorus	0.503 (0.296–0.855)	0.011
Age	1.011 (0.991–1.030)	0.276
Sex (male)	1.051 (0.580–1.906)	0.870
BMI	1.028 (0.962–1.098)	0.412
Model B — Ca/P ratio	2.503 (1.353–4.629)	0.003
Age	1.007 (0.988–1.026)	0.472
Sex (male)	1.123 (0.620–2.036)	0.702
BMI	1.035 (0.969–1.106)	0.306
Model C (compositional) — ilr balance	1.831 (0.084–40.08)	0.701
ilr size	0.037 (0.003–0.535)	0.016
Age / Sex (male) / BMI	1.011 / 1.060 / 1.028	0.284 / 0.847 / 0.410

(B) Robustness and multivariate analyses

Analysis	Result
E-value — Grade$\geq$2 ~ Phosphorus (per SD)	OR 0.70; E-value 1.68
E-value — Grade$\geq$2 ~ Ca/P ratio (per SD)	OR 1.48; E-value 1.73 (CI bound 1.22)
E-value — Grade$\geq$2 ~ ilr balance (per SD)	OR 1.38; E-value 1.63 (CI bound 1.06)
Collinearity (VIF): raw P + Ca/P vs ilr coordinates	4.4 $\rightarrow$ 1.75
Specification curve (32 specifications)	100% same sign; 88% significant; median log-OR 0.368
Mahalanobis (Ca,P) distance across grade	Kruskal–Wallis p=0.033; trend p=0.047
PCA — PC1 (pressure-vs-mineral; 28.6% variance) vs grade	Kruskal–Wallis p<0.001

(C) ROC discrimination — Grade $\geq$ 2 and LVH (n = 170–171)

Outcome	Biomarker	AUC (95% CI)	Youden cut	Sens	Spec
Grade ≥ 2	Calcium	0.568 (0.481–0.656)	8.56	0.43	0.75
	Phosphorus	0.652 (0.570–0.733)	2.95	0.53	0.78
	Ca/P ratio	0.629 (0.546–0.712)	3.22	0.46	0.88
	Ca $\times$ P product	0.638 (0.554–0.722)	25.31	0.45	0.80
LVH	Calcium	0.529 (0.435–0.624)	8.52	0.41	0.72
	Phosphorus	0.565 (0.476–0.653)	3.27	0.79	0.32
	Ca/P ratio	0.561 (0.473–0.648)	2.69	0.76	0.38
	Ca $\times$ P product	0.571 (0.482–0.661)	28.27	0.68	0.46

Penalised LVH models: elastic-net regression shrank all mineral predictors to zero; Firth regression – Ca/P ratio OR 1.57 (0.82–3.13), $p=0.178$; age OR 1.023 (1.002–1.046), $p=0.031$; sex and BMI non-significant. DeLong comparisons among LVH AUCs all non-significant ($p>0.24$).

Figures

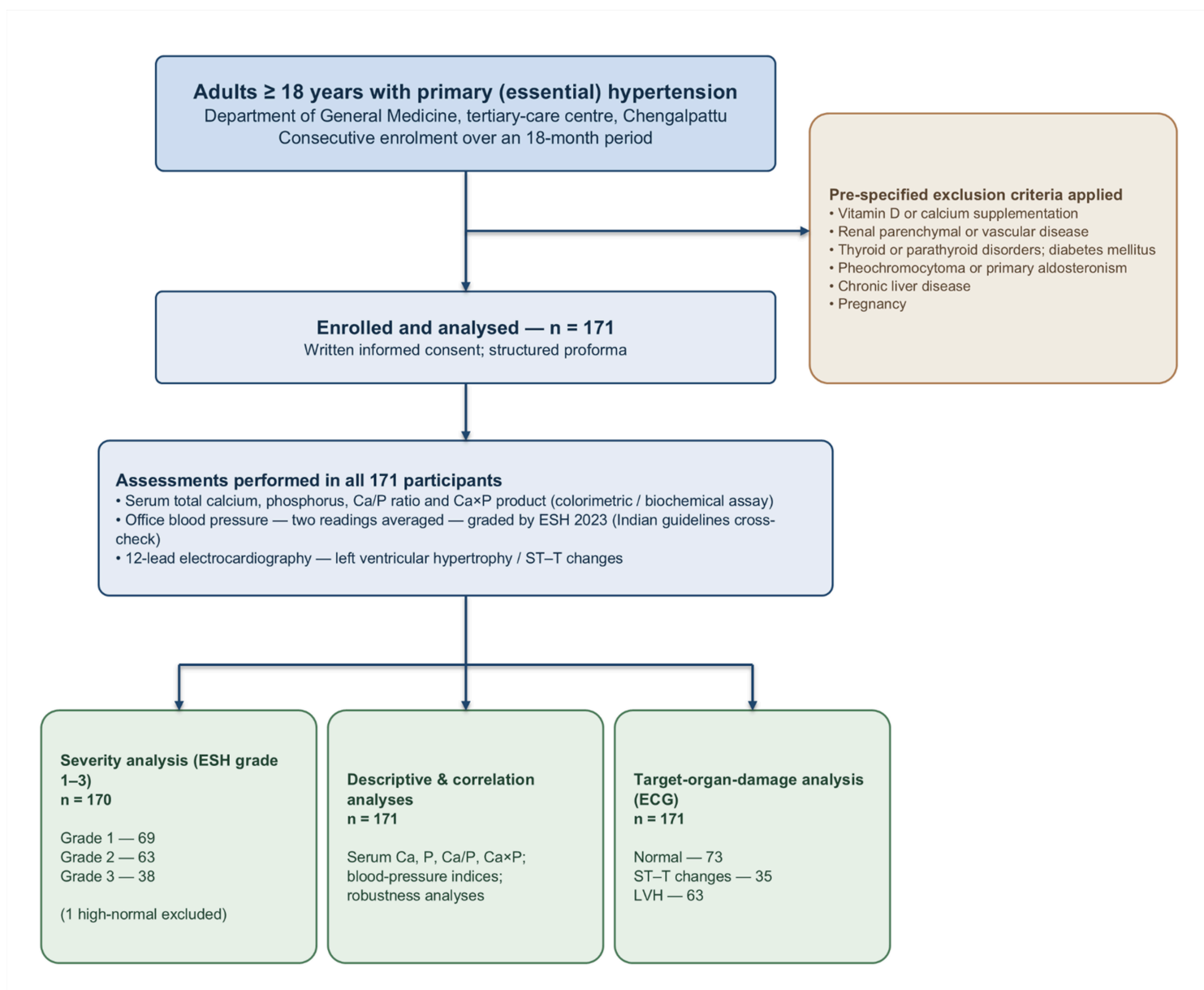


Figure 1

Study flow diagram. Consecutive adults with primary essential hypertension were enrolled after pre-specified exclusions for conditions perturbing calcium–phosphorus homeostasis or causing secondary hypertension. All 171 enrolled participants underwent serum mineral measurement, ESH 2023 blood-pressure grading and 12-lead electrocardiography. The severity analysis was restricted to the 170 grade 1–3 patients (one high-normal excluded); descriptive, correlation and target-organ-damage analyses used the full cohort (n = 171).

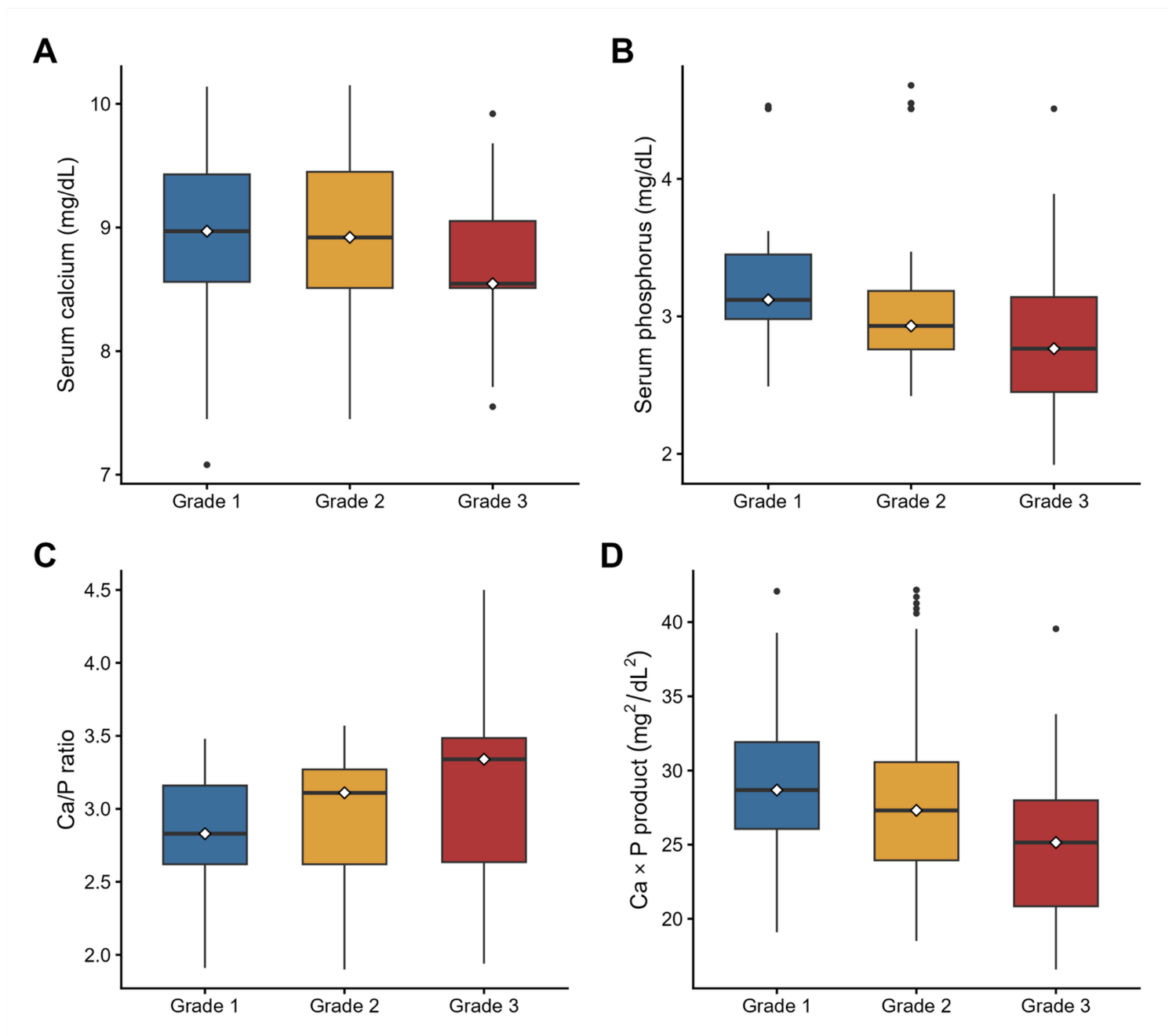


Figure 2

Serum minerals across hypertension severity. Box-and-whisker plots of (A) serum calcium, (B) serum phosphorus, (C) the Ca/P ratio and (D) the Ca×P product across ESH 2023 grades (n = 170). Boxes show median and interquartile range, whiskers the 1.5×IQR, white diamonds the mean. Serum phosphorus and the Ca×P product fell, and the Ca/P ratio rose, monotonically from grade 1 to 3 (Jonckheere–Terpstra trend $p < 0.001$, 0.0002 and 0.0005); calcium showed only a borderline, non-significant decline ($p = 0.050$).

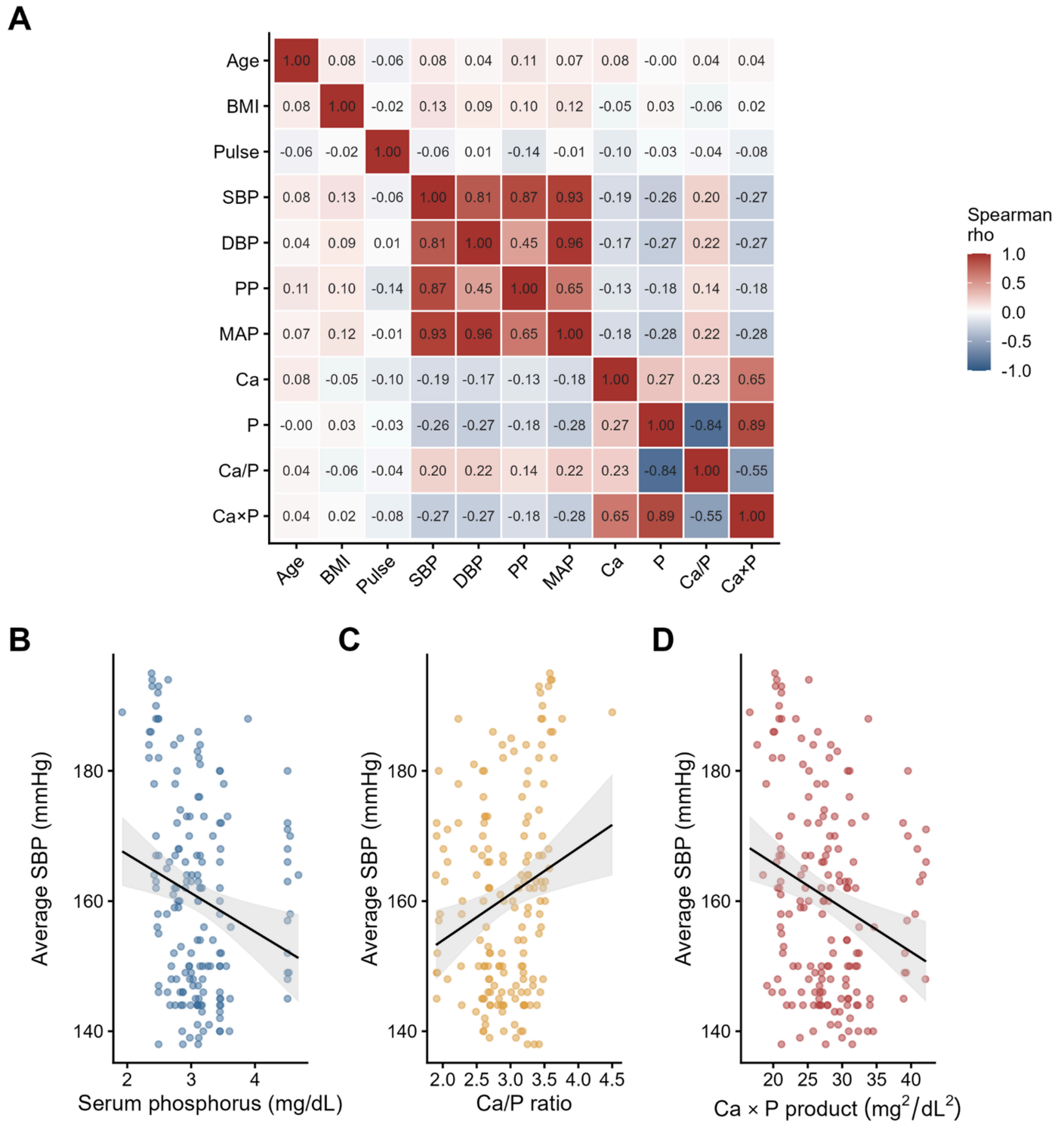


Figure 3

Relationships between serum minerals and blood pressure. (A) Spearman correlation matrix of continuous variables ($n = 171$). (B–D) Scatter plots with linear fit and 95% confidence band for average systolic blood pressure versus (B) serum phosphorus, (C) the Ca/P ratio and (D) the Ca×P product. Phosphorus and the Ca×P product correlated negatively, and the Ca/P ratio positively, with blood pressure (all Benjamini–Hochberg-adjusted $p < 0.05$).

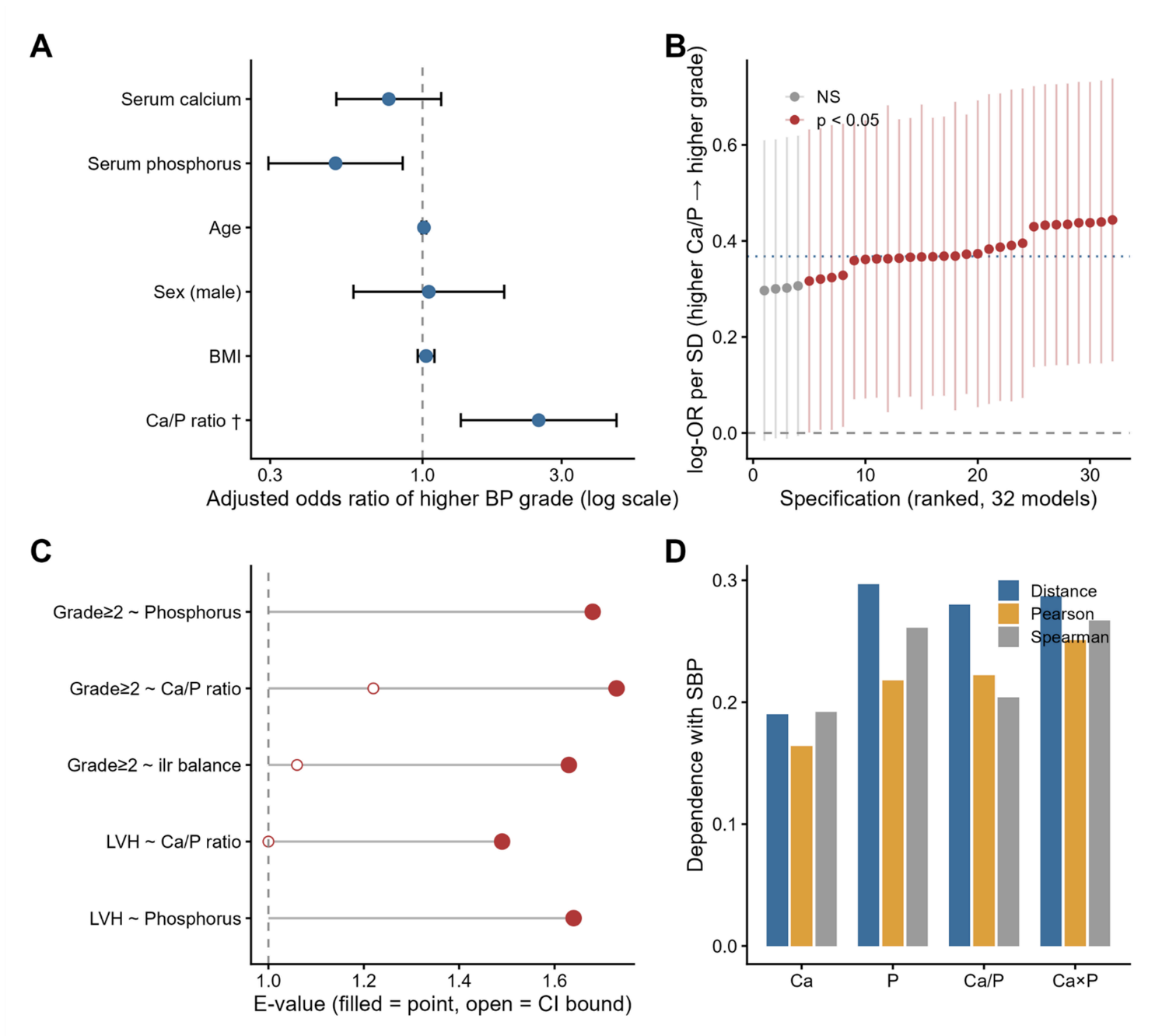


Figure 4

Multivariable model and robustness analyses. (A) Adjusted odds ratios (95% CI) from ordinal proportional-odds regression of blood-pressure grade; † denotes the Ca/P ratio from the collinearity-safe model. (B) Specification-curve analysis across 32 specifications (dotted line, median estimate). (C) E-values for the principal mineral–severity associations (filled, point estimate; open, 95% CI bound). (D) Distance correlation versus absolute Pearson and Spearman coefficients with systolic blood pressure.

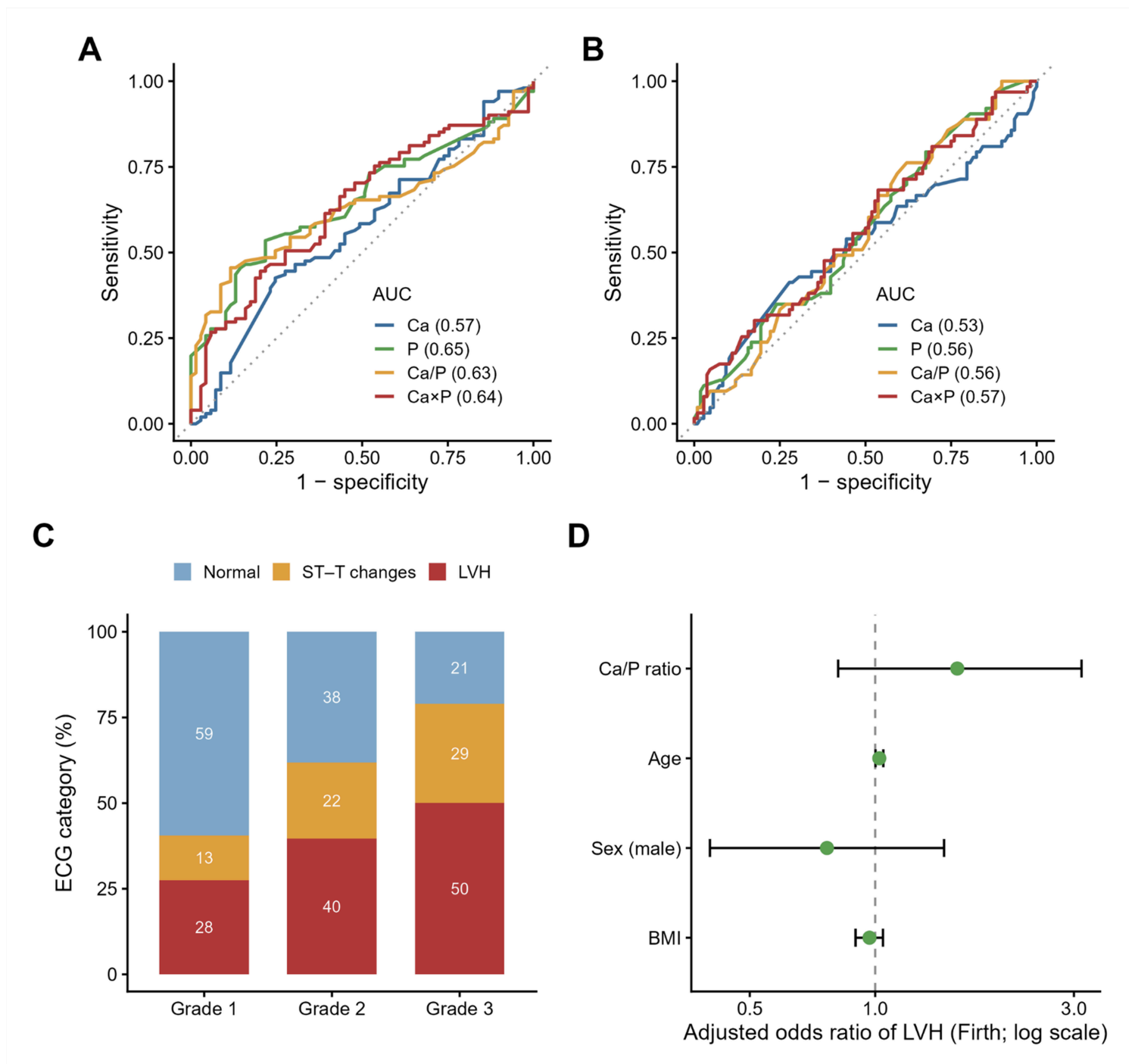


Figure 5

Serum minerals and electrocardiographic target-organ damage. ROC curves for discrimination of (A) grade ≥ 2 hypertension and (B) electrocardiographic LVH (AUC in legend; in-sample estimates). (C) Distribution of ECG categories across blood-pressure grade (Cochran–Armitage trend $p < 0.001$). (D) Adjusted odds ratios (95% CI) for LVH from Firth penalized logistic regression; only older age was associated with LVH.

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