

Impact of Plasma Protein Levels on Electrolyte Measurements

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EXIAS GmbH



Impact of Plasma Protein Levels on Electrolyte Measurements

A Comparative Study of Direct and Indirect Ion-Selective Electrode Methods

M. Schlaminger¹, B. Webb², A. Bartel², T. Niedrist³, M. Herrmann³, H. Scharnagl³

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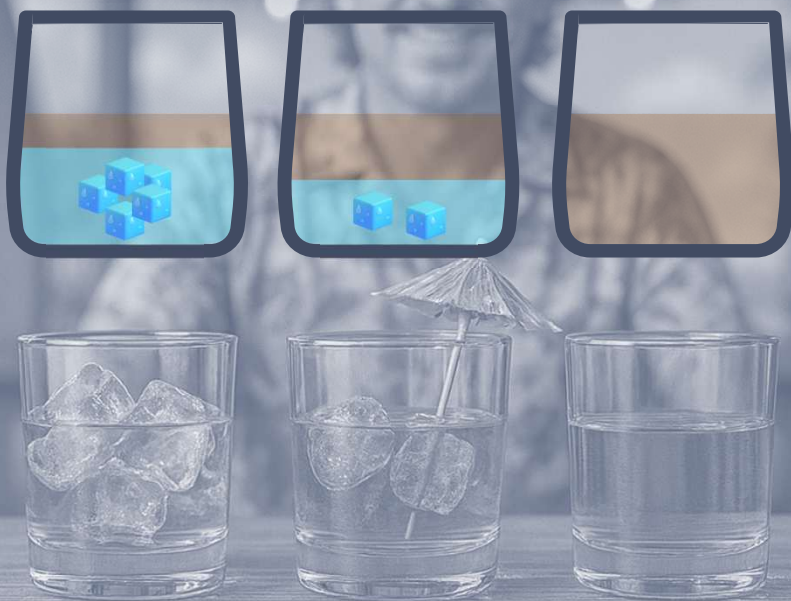




Why am I showing you this picture?

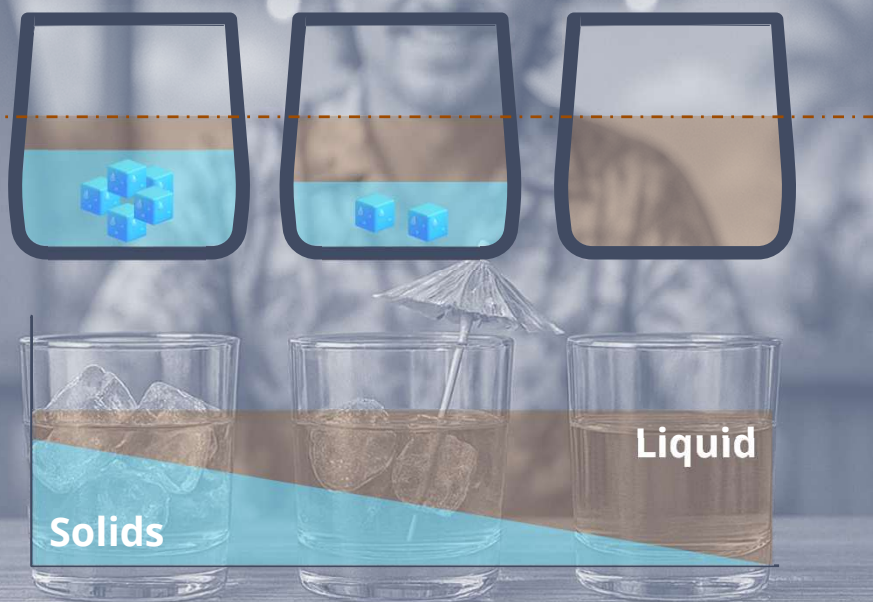
EXIAS

Because solids matter, even when they shouldn't ...



Because solids matter, even when they shouldn't ...

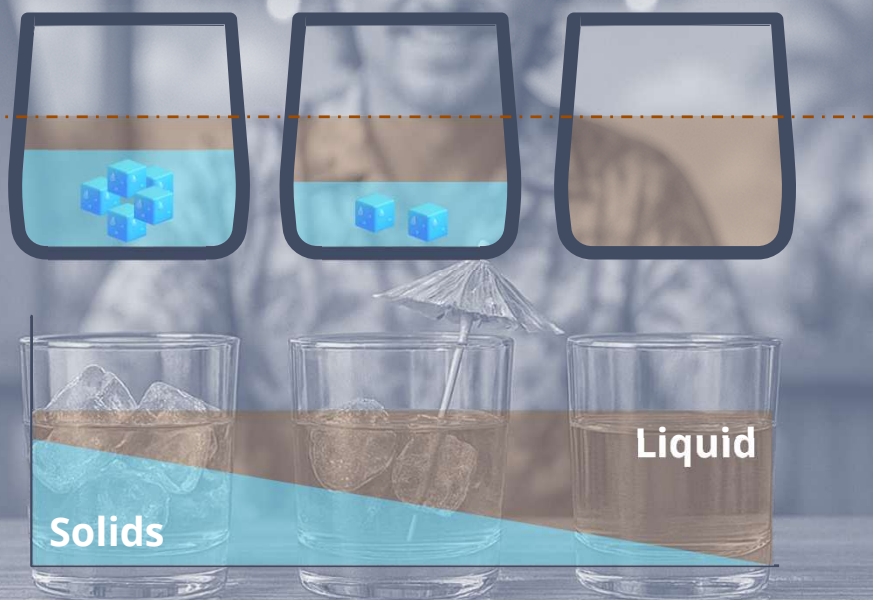
- All glasses are at same level 🍹 – but the drinkable part varies
- The more ice 🧊, the less actual liquid 💧



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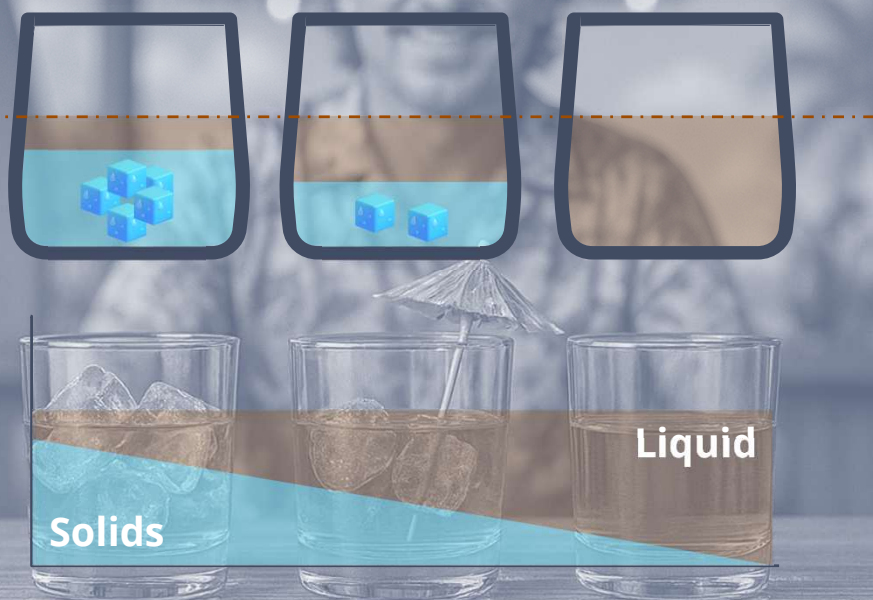
- Ice stands in for non-aqueous solids
- Solids displace water, just like ice displaces the drink



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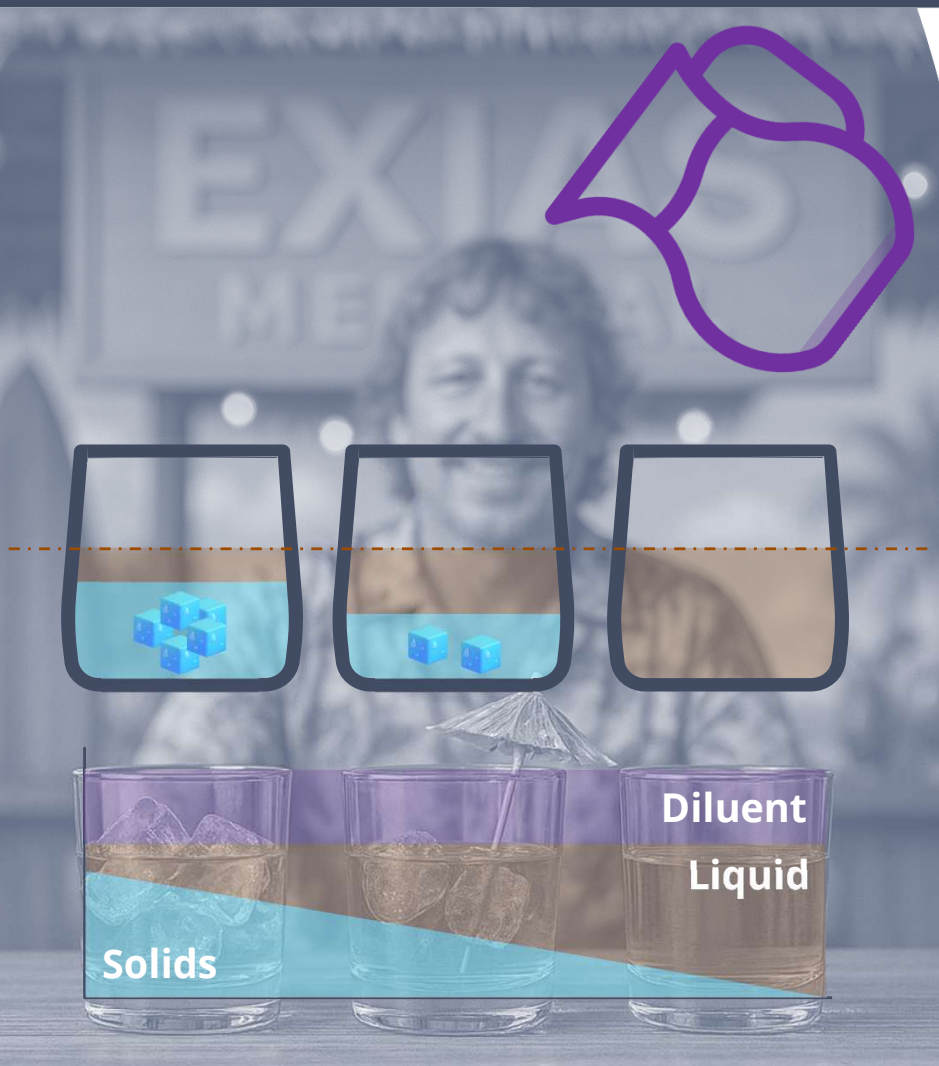
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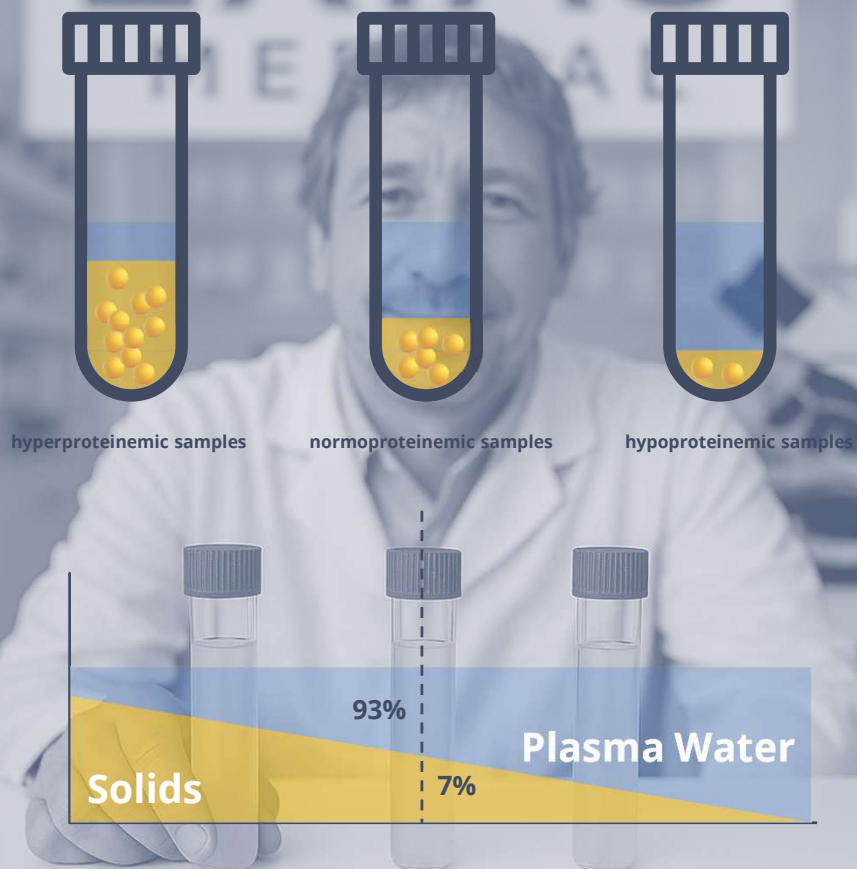
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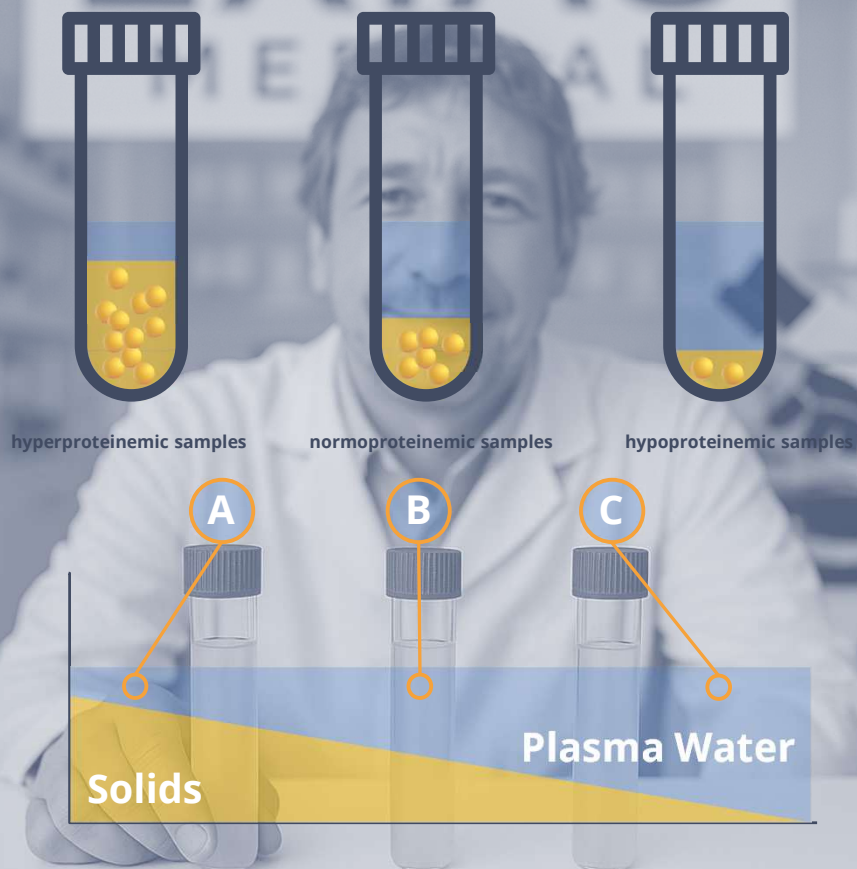


Because solids matter, even when they shouldn't ...



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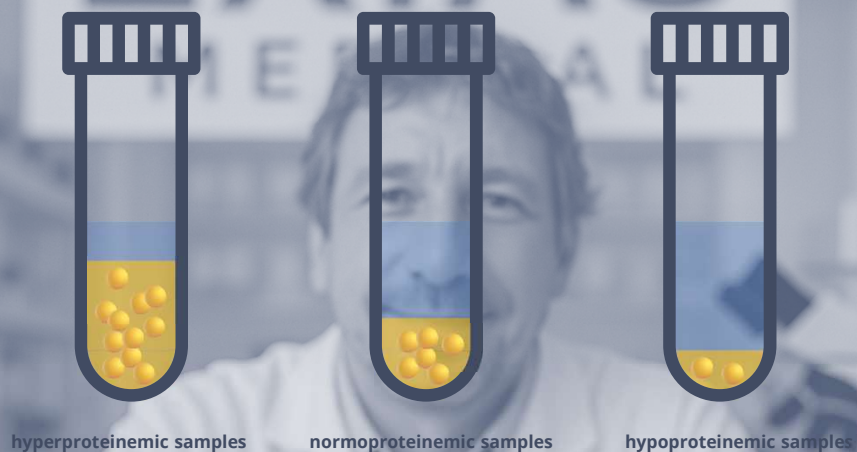
- All tubes are at same level – but the plasma water part varies
- **Electrolytes** are dissolved **only in plasma water**, not in plasma solids
- In a normal plasma:
 - ~93% is water
 - ~7% is solids (lipids, proteins)



Because solids matter, even when they shouldn't ...

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- Electrolytes are dissolved **only in plasma water**, not in plasma solids
- If **measured direct(-ly) in plasma water**:

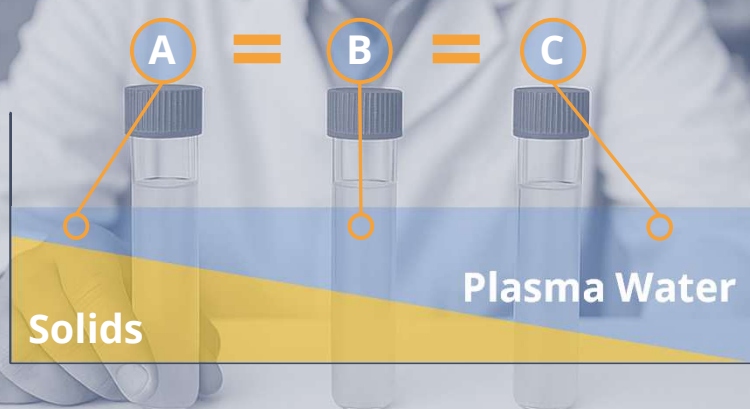




hyperproteinemic samples

normoproteinemic samples

hypoproteinemic samples



Solids

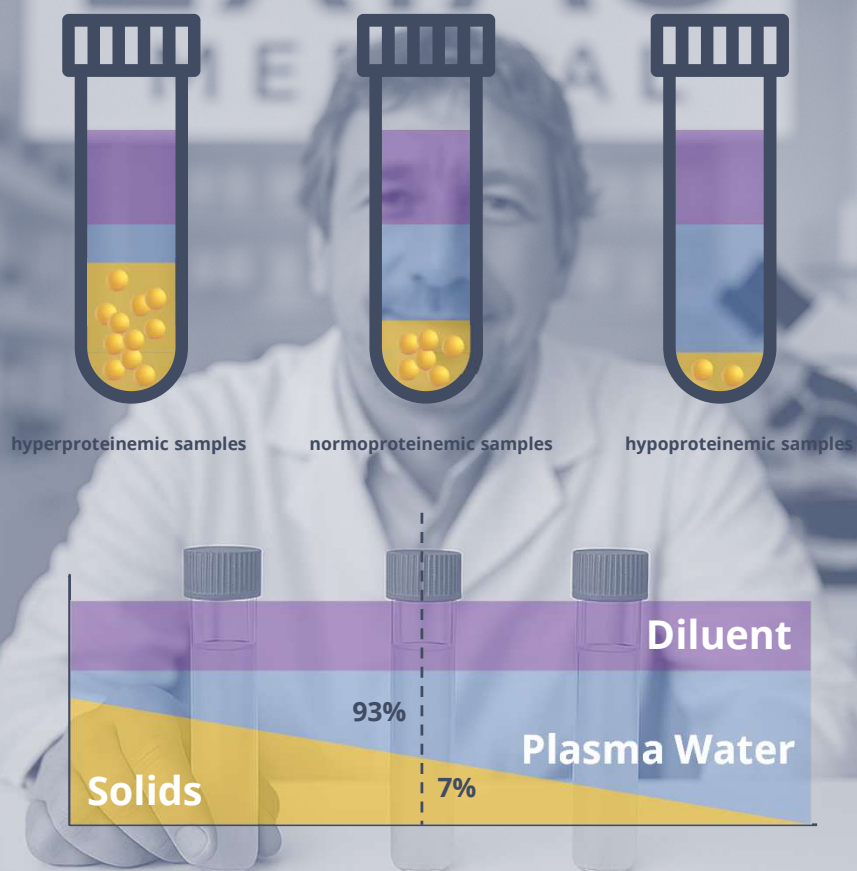
Plasma Water

Because solids ~~even~~ matter, ~~even~~ when they shouldn't ...

don't

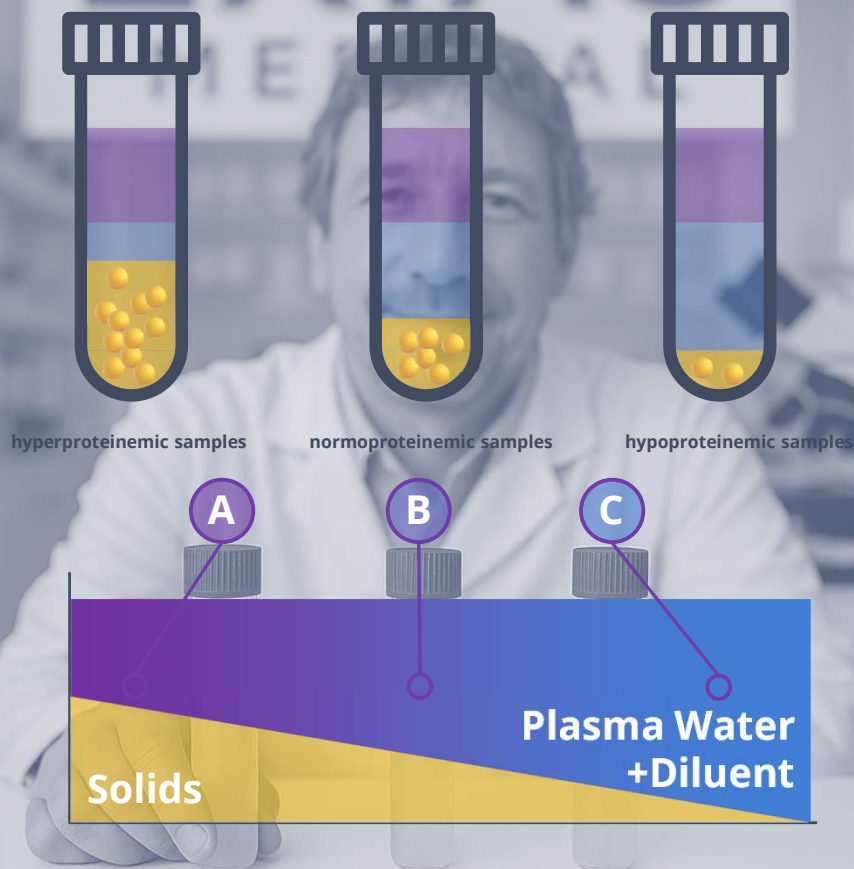
- All tubes are at same level – but the plasma water part varies
- Electrolytes are dissolved **only in plasma water**, not in plasma solids
- If **measured direct(-ly) in plasma water:**

$$A = B = C$$



Because solids matter, even when they shouldn't ...

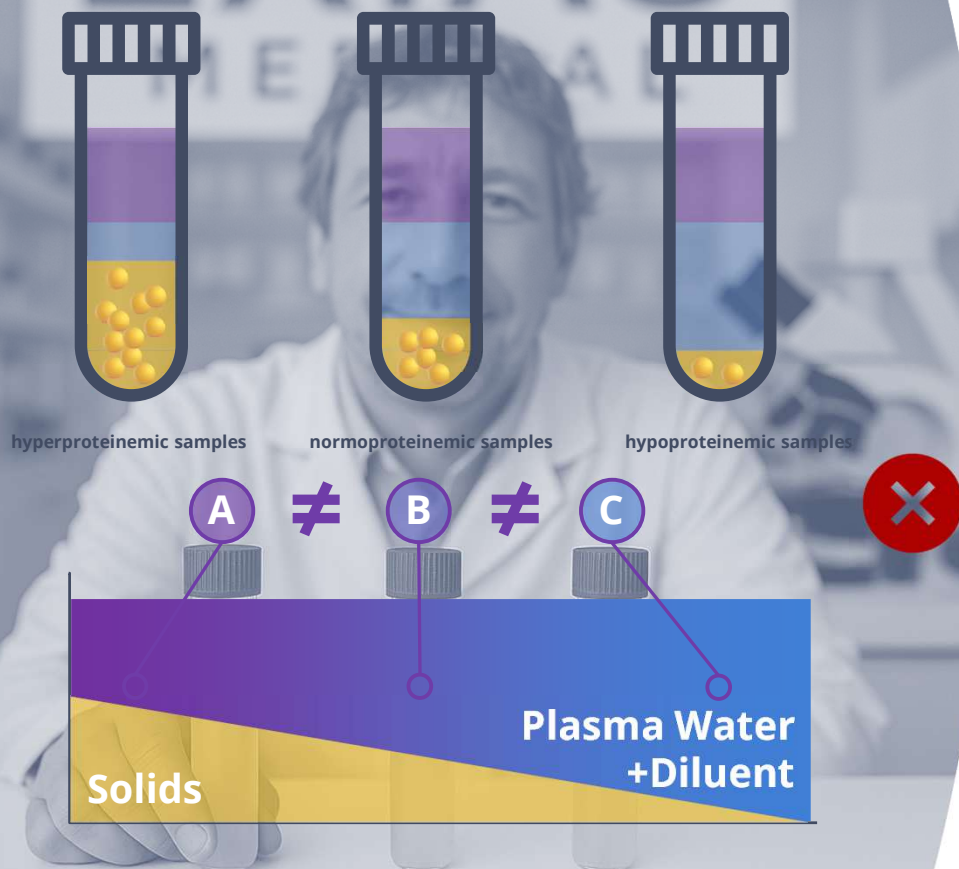
- All tubes are at same level – but the plasma water part varies
 - Electrolytes are dissolved **only in plasma water**, not in plasma solids
 - In a normal plasma:
 - ~93% is water
 - ~7% is solids
- Add Diluent (1:33)



Because solids matter, even when they shouldn't ...

- All tubes are at same level – but the plasma water part varies
- Electrolytes are dissolved **only in plasma water**, not in plasma solids
- If **measured indirect(-ly)** in **diluted sample**:





Because solids matter, even when they shouldn't ...

- All tubes are at same level – but the plasma water part varies
- Electrolytes are dissolved **only in plasma water**, not in plasma solids
- If measured indirect(-ly) in diluted sample:

$$A < B < C$$

Electrolyte Measurement

Summary of Metrological Differences

Direct ISE

VS

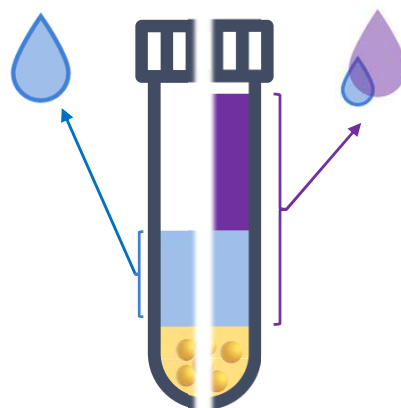
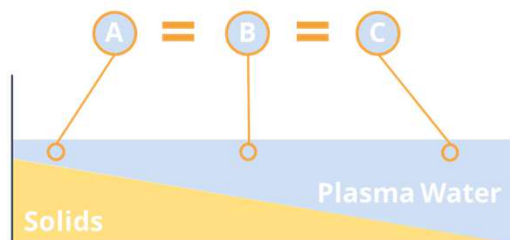
Indirect ISE

Dilution Free

Measures on a **non-diluted sample** (S/P/B).
Actual measurement is performed on the plasma water.

Independent of Solids

Result is **independent of the content of solids**
in the sample.

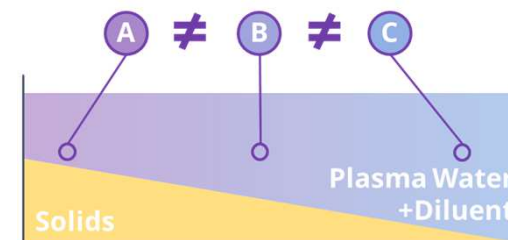


Dilution

Measures on a total sample (S/P, no WB) that has been **diluted with a large volume of diluent**.

Matrix - Effect

Result **depends on the content of solids** in the sample;
i.e., measurements are affected by changes in plasma
protein concentration



(1) Holbek et al. Understanding the different values in electrolyte measurements, acutecaretesting.org; Oct.2002

(2) Dimeski G, Barnett RJ. Effects of total plasma protein concentration on plasma sodium, potassium and chloride measurements by an indirect ion selective electrode measuring system. Crit Care Resusc. 2005 Mar;7(1):12-5. PMID: 16548813

Impact of Plasma Protein Levels on Electrolyte Measurements

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Impact of Plasma Protein Levels on Electrolyte Measurements

Background: Impact of Protein on Electrolyte Measurement

- **Abstract-Focus:** Evaluating the **influence of plasma protein levels** on electrolyte values:
 - **Direct ISE** (no dilution)
 - **Indirect ISE** (diluted samples; assumes normal plasma water fraction)
- **Matrix Effects:**
 - **Indirect ISE** results can be **biased** in hypo-/hyperproteinemic states
 - Pseudohypo- and pseudohyper- effects linked to altered protein content
- **Mechanism:**
 - **Indirect ISE relies on fixed plasma water fraction assumptions**, which break down in abnormal protein conditions

Impact of Plasma Protein Levels on Electrolyte Measurements

Study Overview: Electrolyte Measurement Comparison in Leftover Plasma Samples

- **Study Design:** Method Comparison Study (CLSI EP09-A3)
- **Sample Set:** 120 lithium heparin plasma samples (leftover patient samples)
- **Study Center:** Clinical Institute of Medical and Chemical Laboratory Diagnostics
Medical University of Graz, Austria
- **Sponsor:** MEON Medical Solutions
Graz, Austria



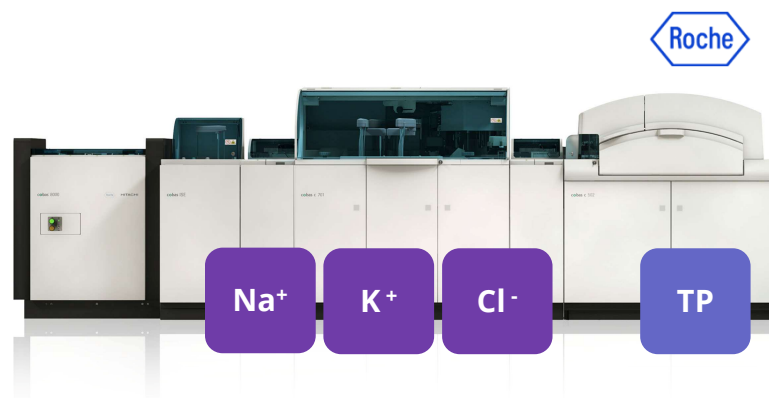
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Study Overview: Electrolyte Measurement Comparison in Leftover Plasma Samples

Direct ISE

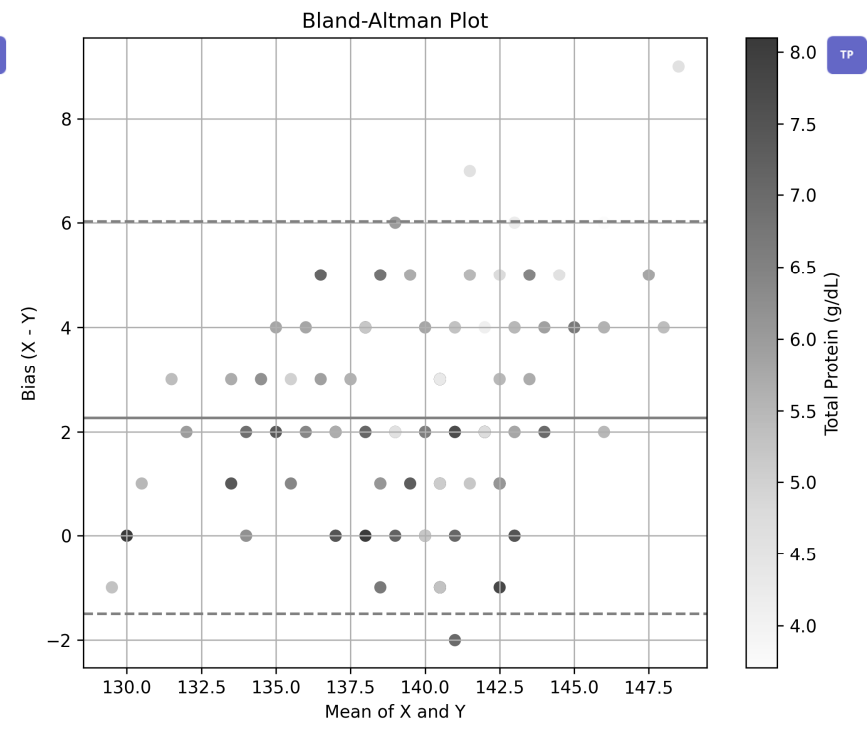
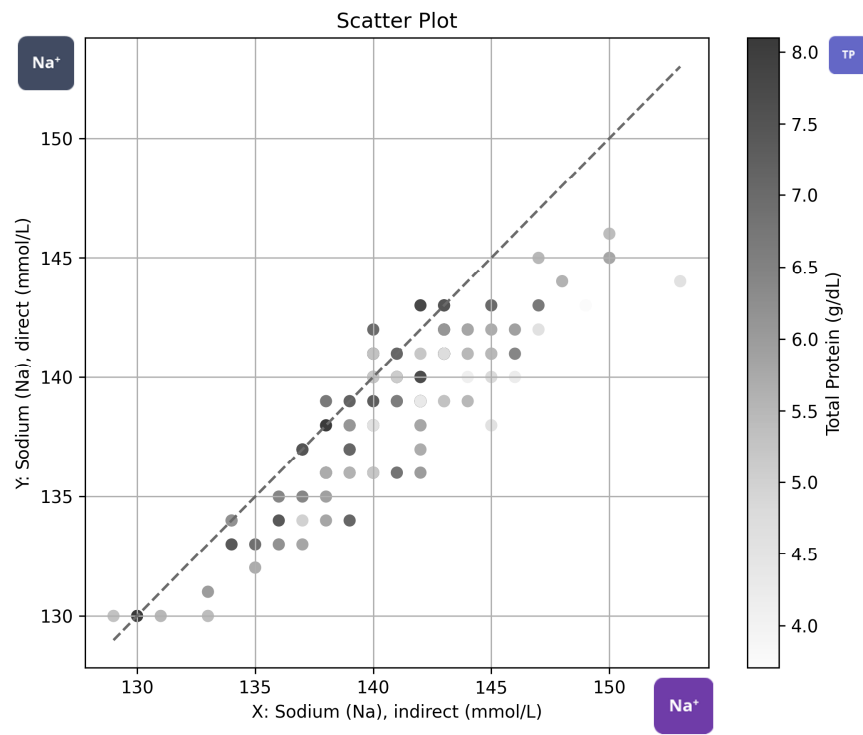
VS

Indirect ISE



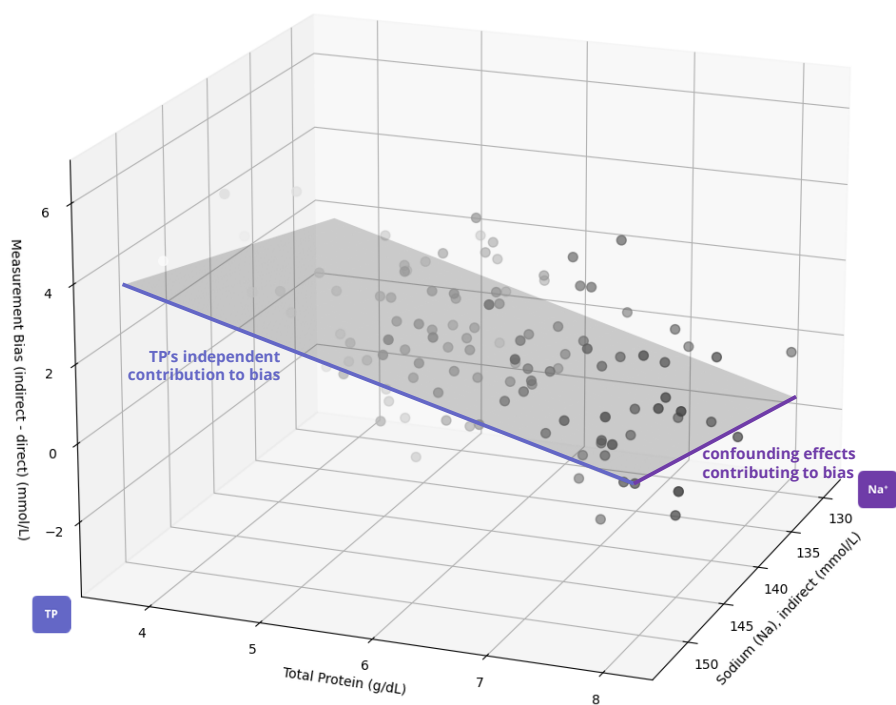
Impact of Plasma Protein Levels on Electrolyte Measurements

Results: Method Comparison (Sodium, Na⁺)



Impact of Plasma Protein Levels on Electrolyte Measurements

Results: Impact Estimation using Multivariate Approach (Sodium, Na⁺)



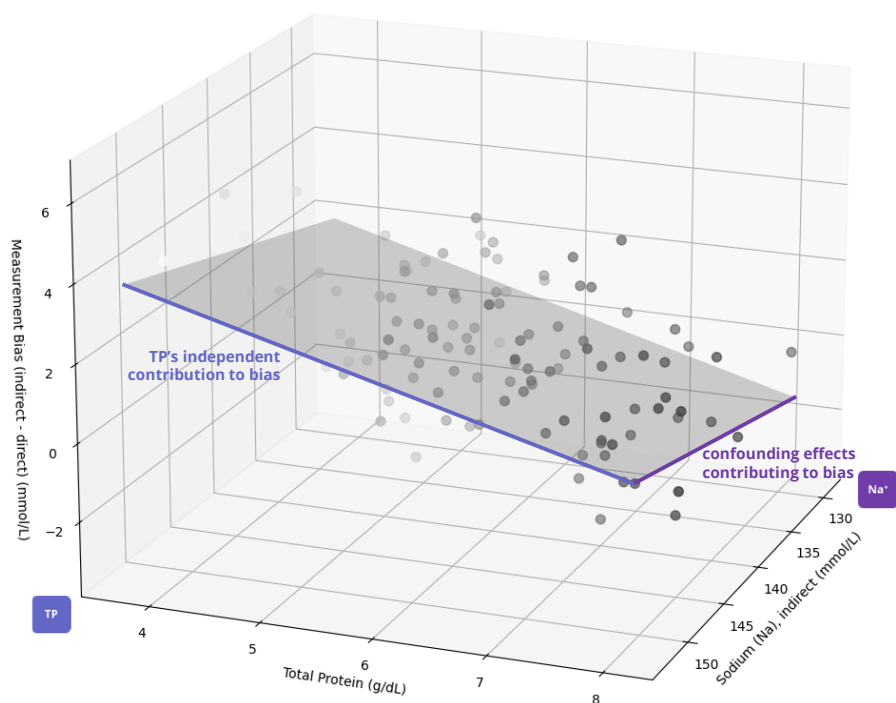
Multivariate Approach:

$$\hat{b} = \underbrace{\beta_2 \cdot TP}_{\substack{\text{TP's independent} \\ \text{contribution to bias}}} + \underbrace{\beta_1 \cdot c_{Na} + \beta_0}_{\substack{\text{Na}^+ \\ \text{confounding effects} \\ \text{contributing to bias}}}$$

Why Use a Multivariate Approach to Estimate TP Effect?

Impact of Plasma Protein Levels on Electrolyte Measurements

Results: Impact Estimation using Multivariate Approach (Sodium, Na^+)



Multivariate Approach:

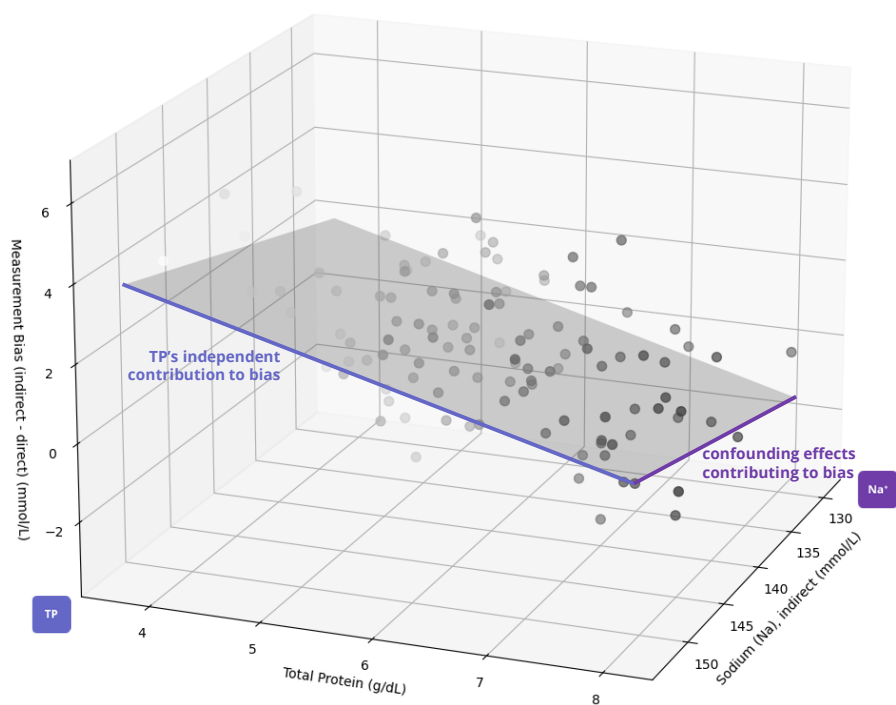
$$\hat{b} = \underbrace{\beta_2 \cdot TP}_{\text{TP's independent contribution to bias}} + \underbrace{\beta_1 \cdot c_{\text{Na}^+} + \beta_0}_{\text{Na}^+ \text{ confounding effects contributing to bias}}$$

Why Use a Multivariate Approach to Estimate TP Effect?

- ↳ Isolates the effect of TP from confounding variables like sodium concentration (x).
- ↳ Quantifies TP's independent contribution to bias, controlling for covariates.
- ↳ Enhances robustness of conclusions!

Impact of Plasma Protein Levels on Electrolyte Measurements

Results: Impact Estimation using Multivariate Approach (Sodium, Na⁺)

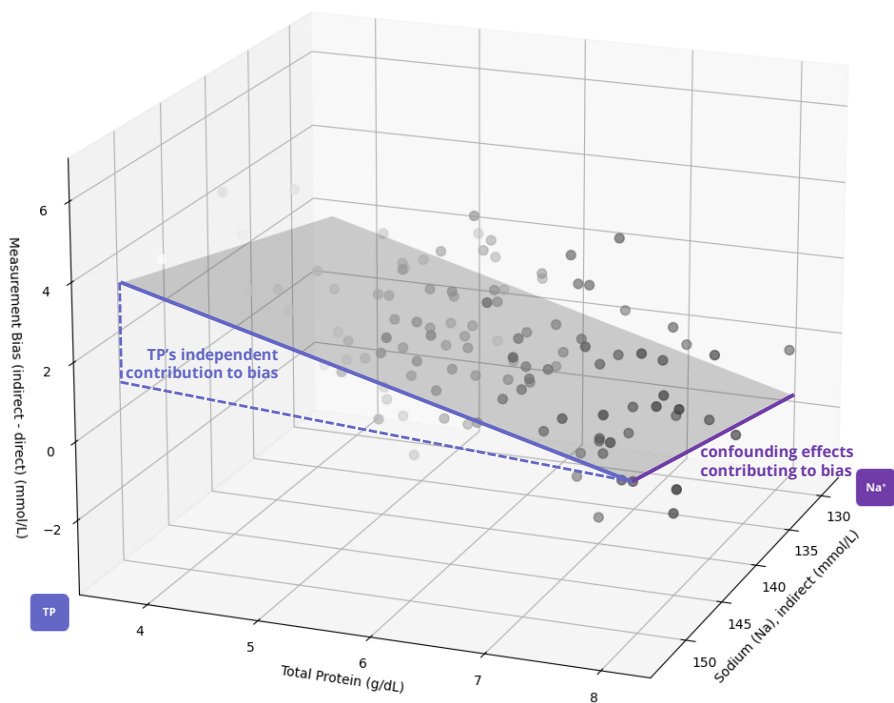


Multivariate Approach:

$$\hat{b} = \underbrace{-0.77 \cdot TP}_{\substack{\text{TP's independent} \\ \text{contribution to bias}}} + \underbrace{0.08 \cdot c_{Na^+}}_{\substack{\text{Na}^+ \\ \text{confounding effects} \\ \text{contributing to bias}}} - 5.9$$

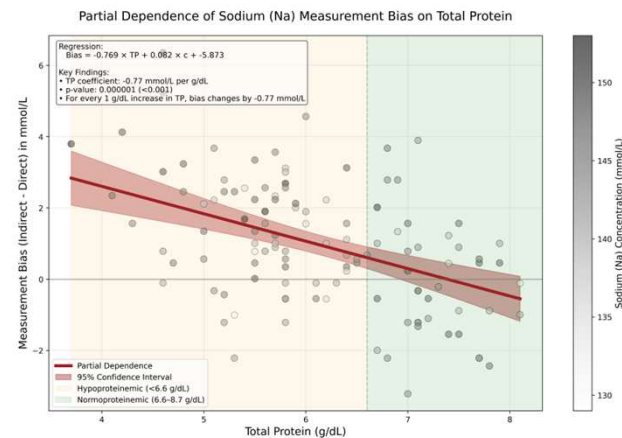
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Multivariate Approach:

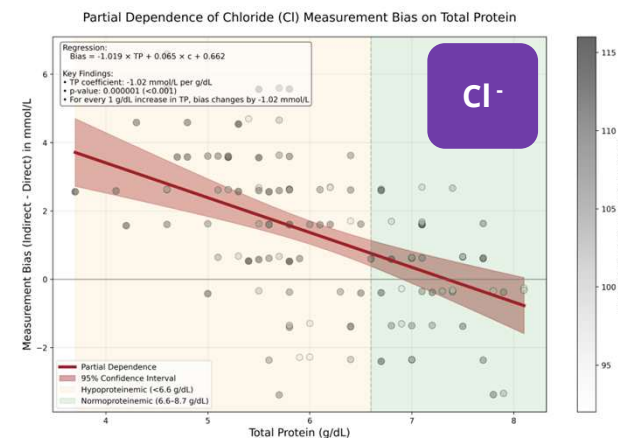
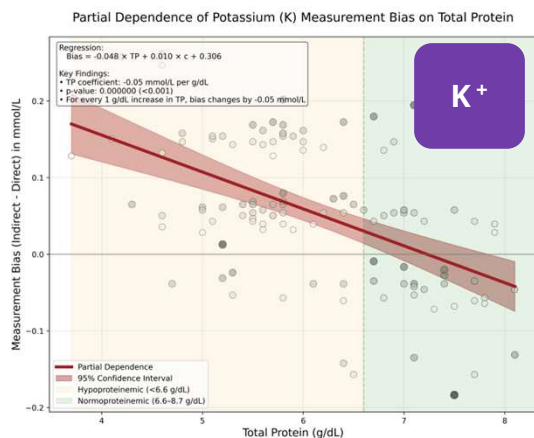
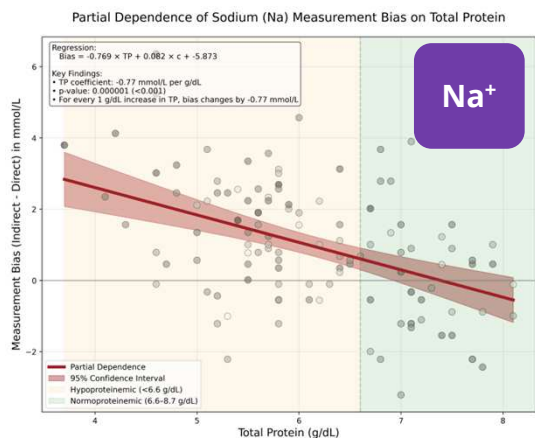
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Impact of Plasma Protein Levels on Electrolyte Measurements

Key Findings: Protein-Dependent Bias in Indirect ISE Measurements

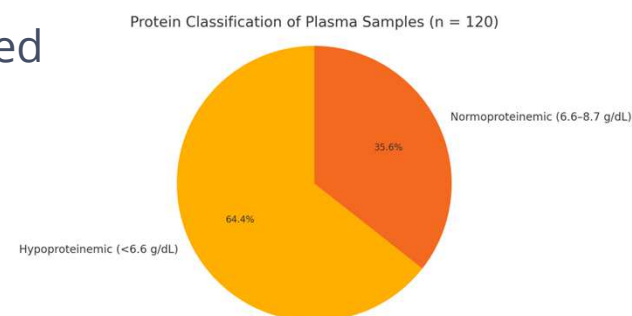
- **Significant biases observed** for Na⁺, K⁺, and Cl⁻ (all p < 0.05)
 - Na⁺: -0.77 mmol/L (p < 0.001)
 - K⁺: -0.05 mmol/L (p < 0.001)
 - Cl⁻: -1.02 mmol/L (p < 0.001)



Impact of Plasma Protein Levels on Electrolyte Measurements

Key Findings: Protein-Dependent Bias in Indirect ISE Measurements

- **Interpretation:**
 - Indirect ISE **overestimates** in hypoproteinemia (→ pseudohyper-)
 - Indirect ISE **underestimates** in hyperproteinemia (→ pseudohypo-)
- **Observed biases aligned with theoretical predictions** based on plasma water fraction.
- **Biases were solely attributable to TP**, confirmed by multivariate correction
- **Limitation:** No hyperproteinemic samples (>8.7 g/dL) included



Impact of Plasma Protein Levels on Electrolyte Measurements

Interpretation & Clinical Implications

- **Study confirms previous findings** (Dimeski et al.):
 - Na^+ bias of -0.77 mmol/L per g/dL TP matches prior estimates -0.78 to -0.98

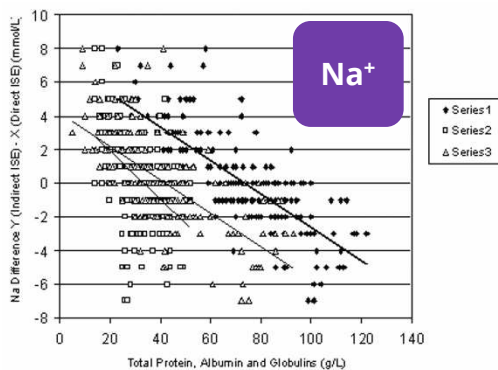


Figure 1. The relationship between the differences of direct minus indirect ion selective electrode results for sodium versus variable total protein concentrations. ♦ - total protein, □ - albumin, △ - globulins.

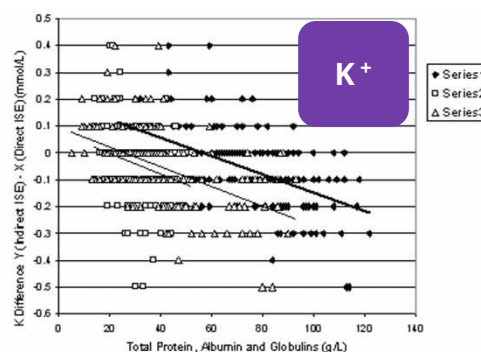


Figure 2. The relationship between the differences of direct minus indirect ion selective electrode results for potassium versus variable total protein concentrations. ♦ - total protein, □ - albumin, △ - globulins.

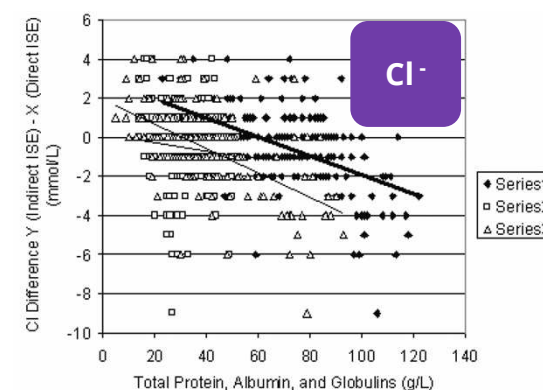


Figure 3. The relationship between the differences of direct minus indirect ion selective electrode results for chloride versus variable total protein concentrations. ♦ - total protein, □ - albumin, △ - globulins.

(1) Dimeski G, Barnett RJ. Effects of total plasma protein concentration on plasma sodium, potassium and chloride measurements by an indirect ion selective electrode measuring system. Crit Care Resusc. 2005 Mar;7(1):12-5. PMID: 16548813

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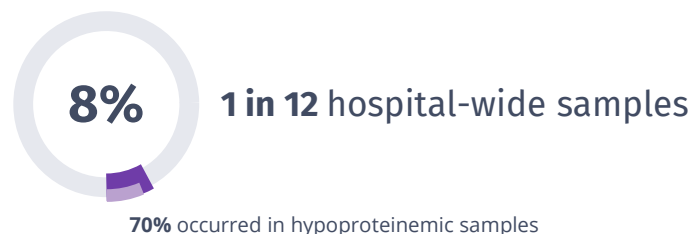
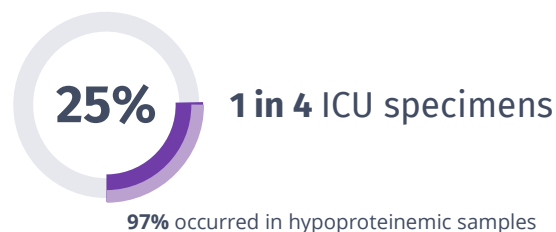
Interpretation & Clinical Implications

- **Indirect ISE methods are vulnerable** to protein-related matrix effects due to sample dilution and compensation.
- **Clinically relevant impact:** Particularly affects sodium measurements in critically ill patients with abnormal protein levels
- The observed coefficient aligns well with previous estimates supporting the **consistency of this phenomenon across different analytical platforms.**

Impact of Plasma Protein Levels on Electrolyte Measurements

Interpretation & Clinical Implications

Indirect ISE specimen affected by Matrix Effects

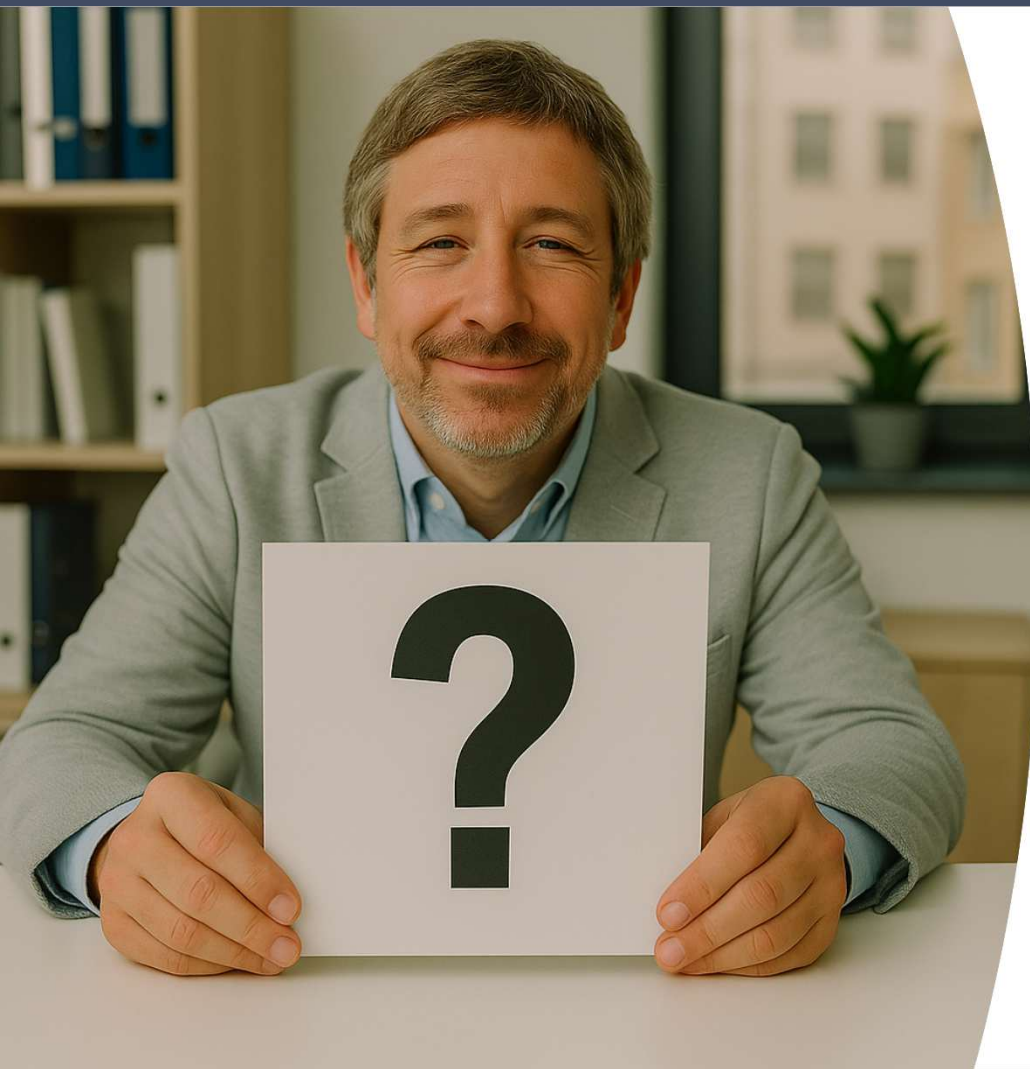


Indirect ISE

*“Clinicians must be aware that differences exist between the ISE technologies and in border-line clinical situations, the **direct ISE systems provide a more accurate** estimate of plasma sodium, potassium, chloride,... and should be used for clinical decision-making.”*

(Langelaan et. al)

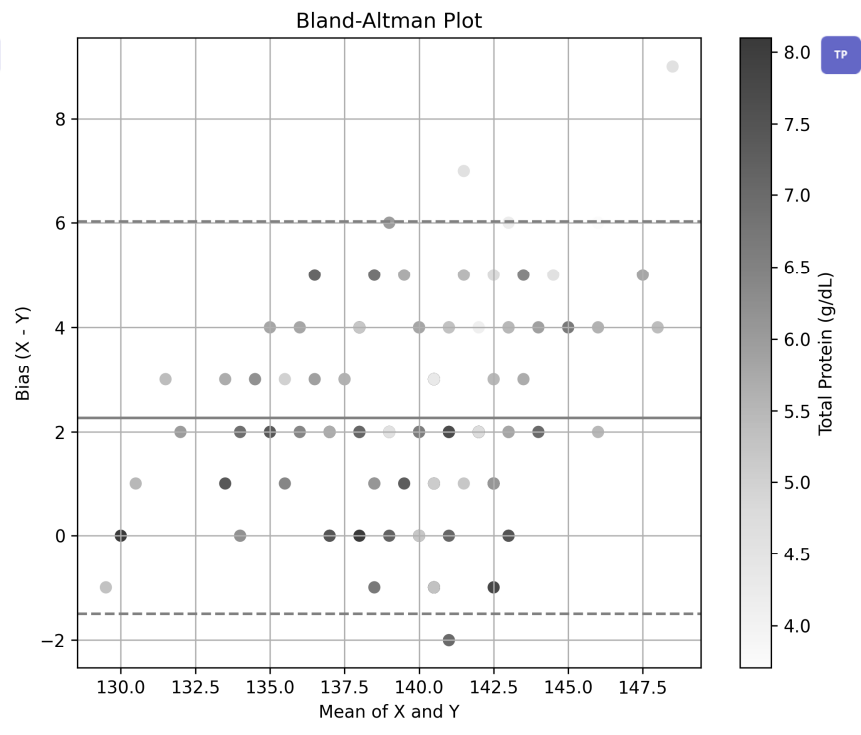
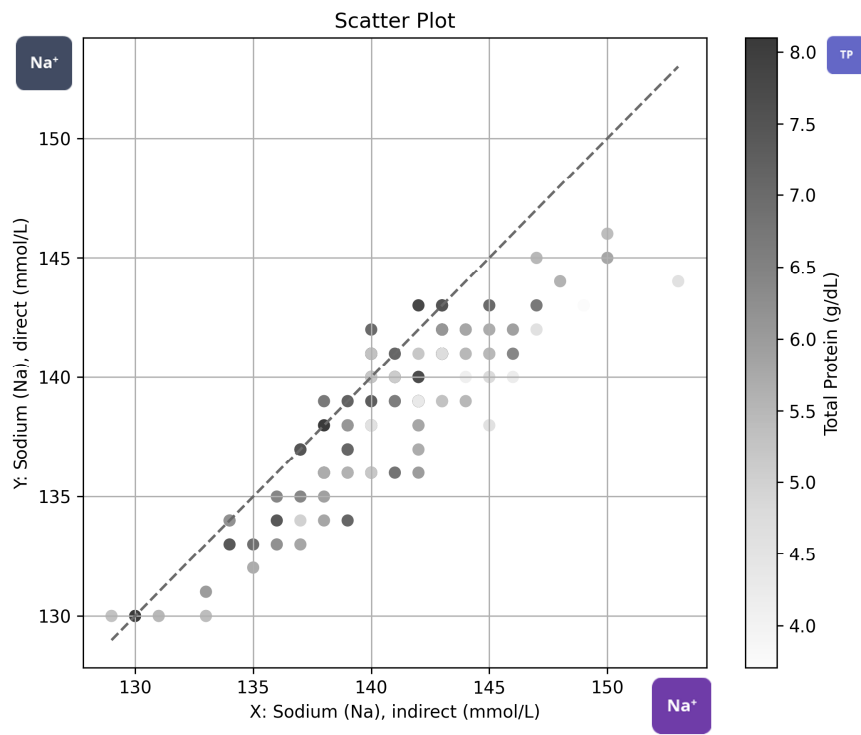
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 (2) Dimeski G, Morgan TJ, Presneill JJ, Venkatesh B. Disagreement between ion selective electrode direct and indirect sodium measurements: estimation of the problem in a tertiary referral hospital. J Crit Care. 2012 Jun;27(3):326.e9-16. doi: 10.1016/j.jcrc.2011.11.003. Epub 2012 Jan 9. PMID: 22227082.
 (3) Langelaan ML, Kamp L, Zandijk E, Rajmakers MT. Prevalence of pseudonatremia in a clinical laboratory - role of the water content. Clin Chem Lab Med. 2017 Mar 1;55(4):546-553. doi: 10.1515/ccdm-2016-0401. PMID: 27676606.



I am no clinician, why should I care?

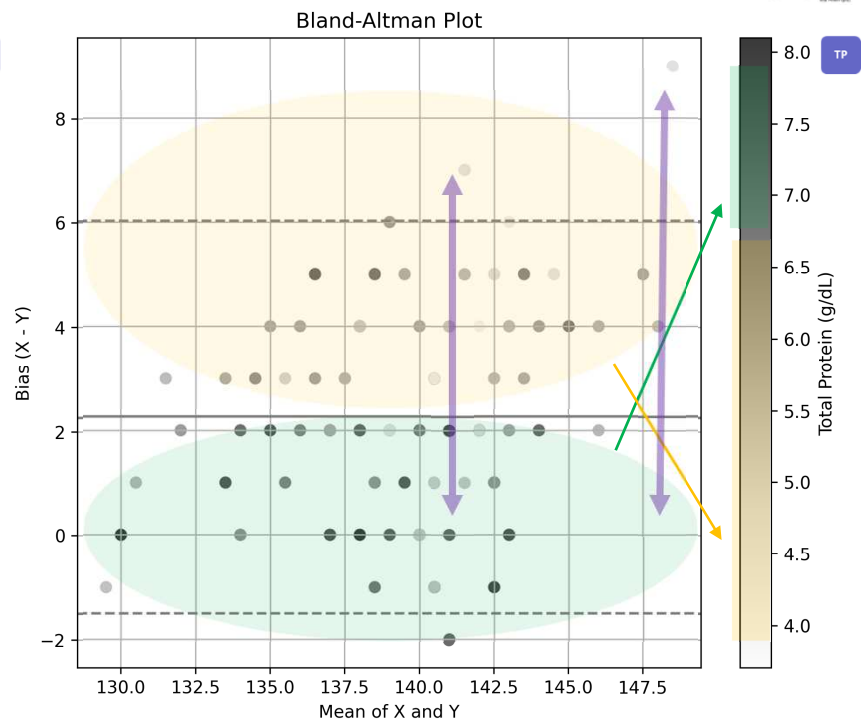
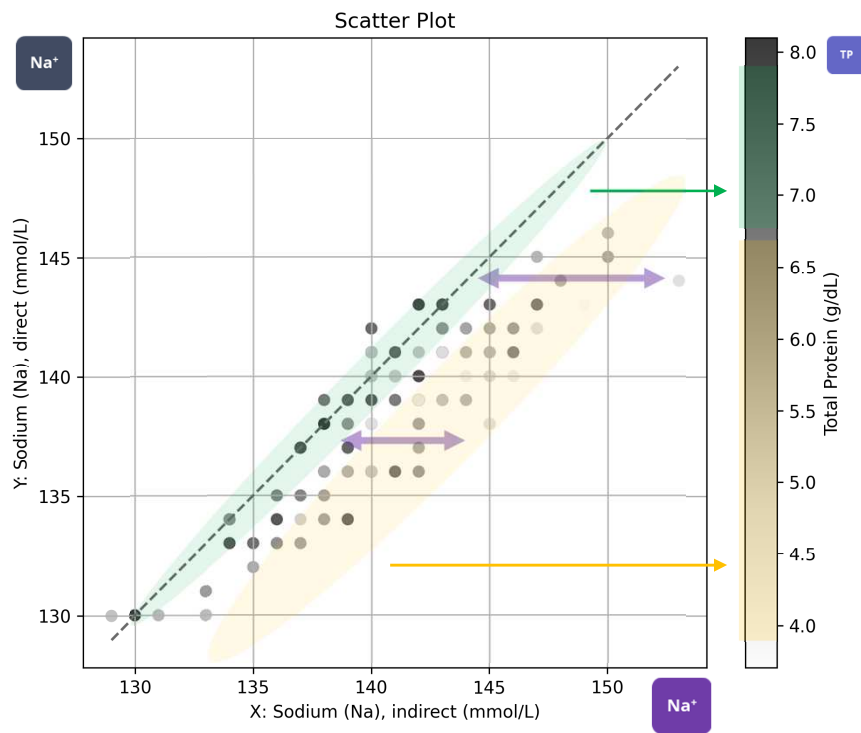
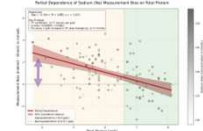
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Study: Method Comparison (Sodium)



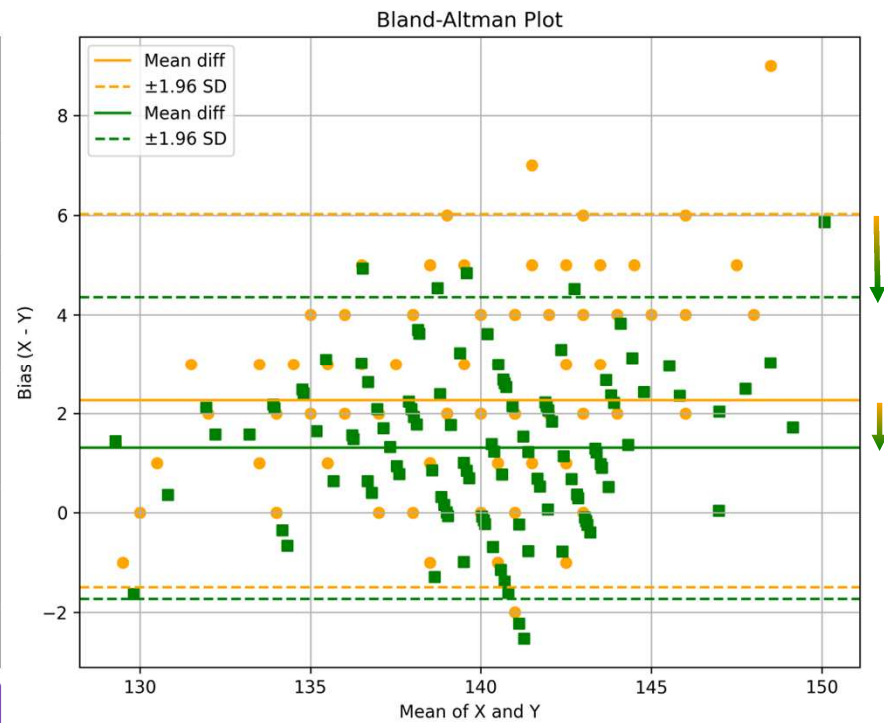
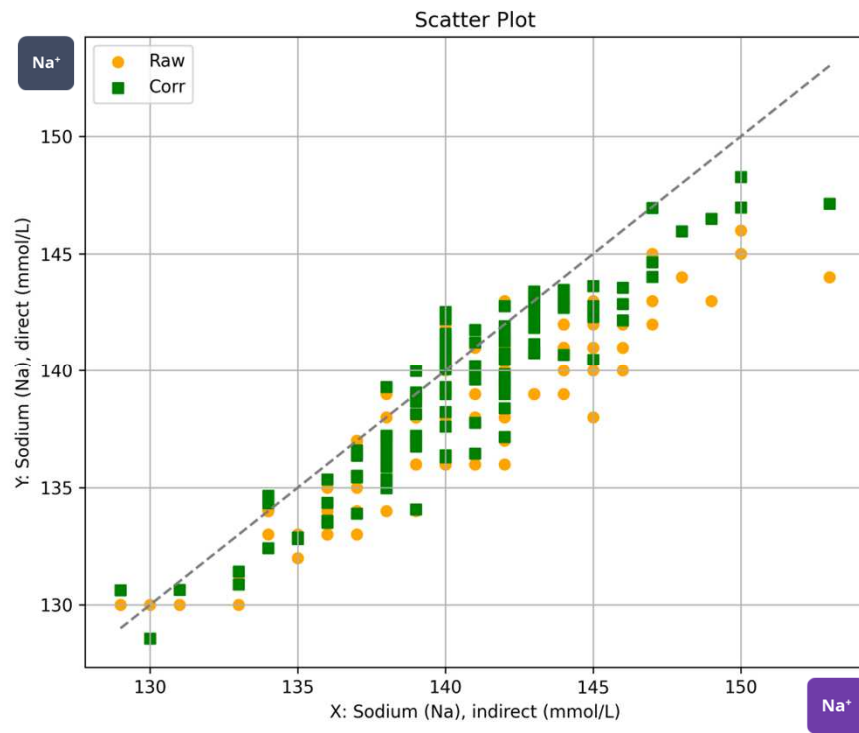
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Study: Method Comparison (Sodium)



Impact of Plasma Protein Levels on Electrolyte Measurements

Study: Method Comparison (Sodium), TP Correction on Indirect Sodium



Impact of Plasma Protein Levels on Electrolyte Measurements

Study: Method Comparison (Sodium)

Impact of TP Correction on Indirect Measurement

- **Reduces systematic bias** introduced by variations in total protein (TP).
- **Minimizes scatter, improving precision** and reliability across patient samples.
- **Enhances agreement with direct methods**, supporting clinical consistency.

Impact of Plasma Protein Levels on Electrolyte Measurements

Study: Method Comparison (Sodium)

Impact of TP Correction on Indirect Measurement

- **Reduces systematic bias** introduced by variations in total protein (TP).
- **Minimizes scatter, improving precision** and reliability across patient samples.
- **Enhances agreement with direct methods**, supporting clinical consistency.

Effect of TP on Comparison Direct with Indirect Measurement

- ⚠ **Systematic bias** due to total protein (TP) variation.
- ⚠ **Increased scatter, reducing precision and reliability across samples.**
- ⚠ **Worsened agreement with direct methods**, potentially affecting decisions.

Impact of Plasma Protein Levels on Electrolyte Measurements

Key Takeaways

- **Direct ISE provides accurate electrolyte results** regardless of protein levels, eliminating matrix effects that can compromise indirect ISE.
- In labs handling critically ill, ICU, or malnourished patients, this means **fewer misclassifications, less rework, and higher trust in results.**
- **Indirect ISE bias complicates method comparison**—affects agreement with direct ISE.





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