



Impact of the 2024 ICSH Guidelines on Interpretation of Coagulation Mixing Studies in Routine Practise.

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INTRODUCTION

Mixing Studies are often to evaluate unexplained prolongation of activated partial thromboplastin (APTT), prothrombin time (PT) or both. They can assist in differentiating coagulation factor deficiencies from inhibitors, but interpretation is complicated by intermediate or borderline results. Locally, interpretive heterogeneity has been observed.

The 2024 International Council for Standardization in Haematology (ICSH) guidelines have proposed standardised use of Rosner Index (RI) or percentage correction (PC), and subtraction analysis to improve interpretive consistency.

This study will retrospectively apply the ICSH 2024 algorithm to mixing studies performed between 2021 and 2025 to evaluate its impact on interpretation and diagnostic outcomes (either inhibitor associated, factor deficiency or equivocal).

AIM

To evaluate how the application of the 2024 ICSH guidelines would influence interpretation of mixing studies.

METHOD

A retrospective review of APTT mixing studies performed from 2021 to 2025 at Northern Pathology Victoria, Australia, was undertaken.

Results were reinterpreted according to the 2024 ICSH guidelines (Fig 1, Table 1) and correlated with lupus anticoagulant and intrinsic factor assays.

PC $\geq$ 70% or RI $\leq$ 15% indicates a likely FD but to be followed through with incubated analysis.

PC< 70% or RI> 15%, if the subtraction analysis is $\geq$ 0, an inhibitor is likely. If not, results must be interpreted post incubated analysis.

RESULTS

A total of 213 APTT mixing studies were analysed. 87 (41%) had RI >15% and 126 (59%) had RI $\leq$ 15%. 159 (74.6%) had PC <70% and 54 (25.4%) had PC $\geq$ 70%. None of the 213 mixing studies had a subtraction value <0. 84 cases of RI>15% had PC<70% (96.6%) whereas, only 51 cases of RI<15% had a PC>70% (40.5%). A comparison of PC and RI using subtraction method as per guidelines showed a 62.9% concordance between the two methods for the immediate mix phase and only 54.5% concordance between the two for the incubated mixing phase.

For the RI >15% group (Figure 3), 45/87 (51.7%) proceeded to LA testing of which 25/45 (55.6%) were positive and 19/87 (10.3%) proceeded to factor testing of which 8/19 (42.1%) were deficient (multifactor). For the RI $\leq$ 15% group (Figure 3) 29/126 (23.0%) proceeded to LA testing of which 9/29 (31.0%) were positive and 47/126 (37.3%) proceeded to factor testing of which 17/47 (36.2%) were deficient (multifactor).

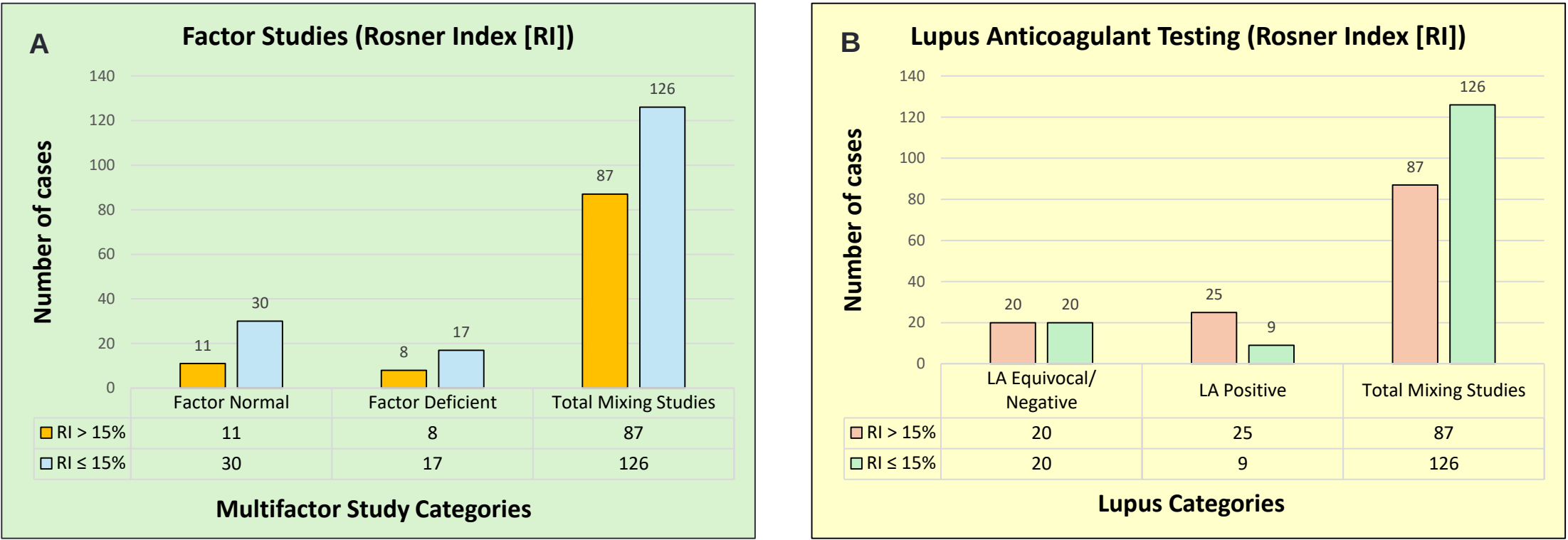


Figure 3. Rosner Index (RI) comparison for factor study (A) and lupus anticoagulant (B) testing on APTT mixing studies.

	LUPUS ANTICOAGULANT	FACTOR DEFICIENCY
Number of tests performed	74	66
Lupus Positive/ Factor Deficient	34	25
Rosner Index>15%	25/74 (33.8%) Sensitivity = 73.5% Specificity = 58.3% PPV = 83.3% NPV = 43.8%	8/66 (12.1%) *
Rosner Index $\leq$ 15%	9/74 (12.2%)	17/66 (25.8%) Sensitivity = 36.2% Specificity = 57.9% PPV = 68.0% NPV = 26.8%

*All were multi-factor deficiencies suggestive of unlikely true deficiency.

Table 2. Sensitivity, specificity, PPV and NPV of RI for lupus inhibitor and factor deficiency.

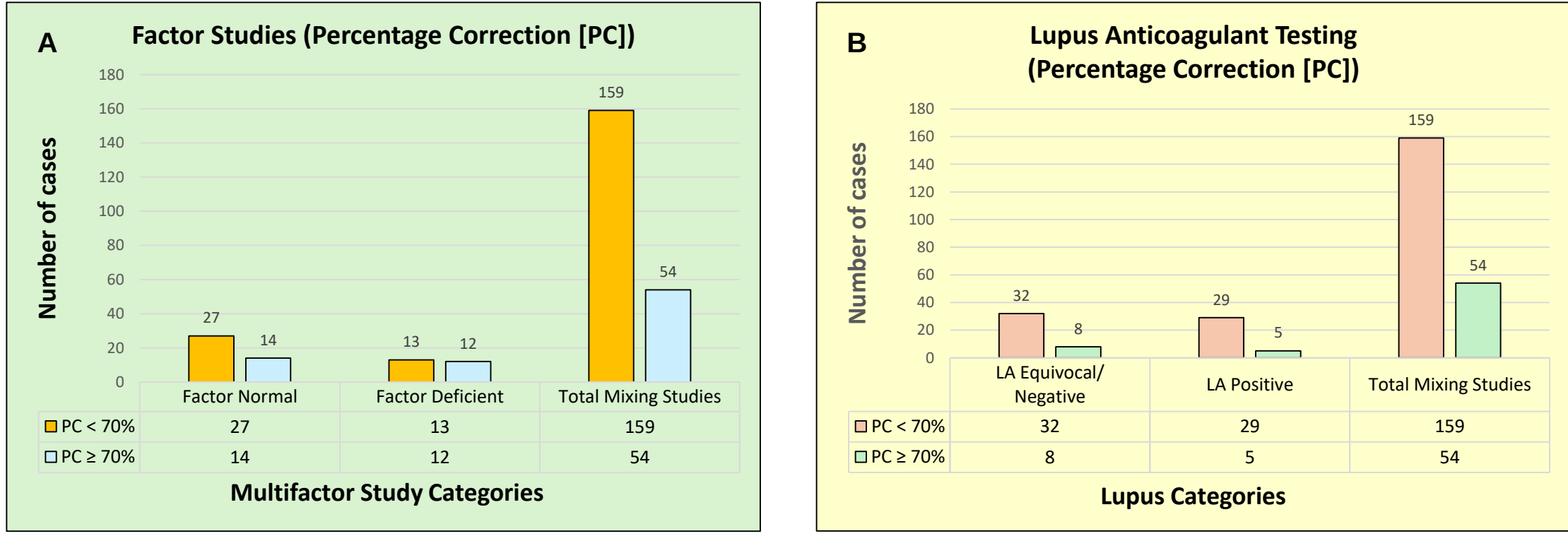


Figure 4. Percentage Correction(PC) comparison for factor study (A) and lupus anticoagulant (B) testing on APTT mixing studies.

	LUPUS ANTICOAGULANT	FACTOR DEFICIENCY
Number of tests performed	74	66
Lupus Positive/ Factor Deficient	34	25
Percentage Correction <70%	29/74 (39.2%) Sensitivity = 72.5% Specificity = 16.7% PPV = 85.3% NPV = 8.3%	13/66 (19.7%) *
Percentage Correction $\geq$ 70%	5/74 (6.8%)	12/66 (18.2%) Sensitivity = 46.2% Specificity = 67.5% PPV = 48.0% NPV = 65.9%

*All were multi-factor deficiencies suggestive of unlikely true deficiency.

Table 3. Sensitivity, specificity, PPV and NPV of PC for lupus inhibitor and factor deficiency.

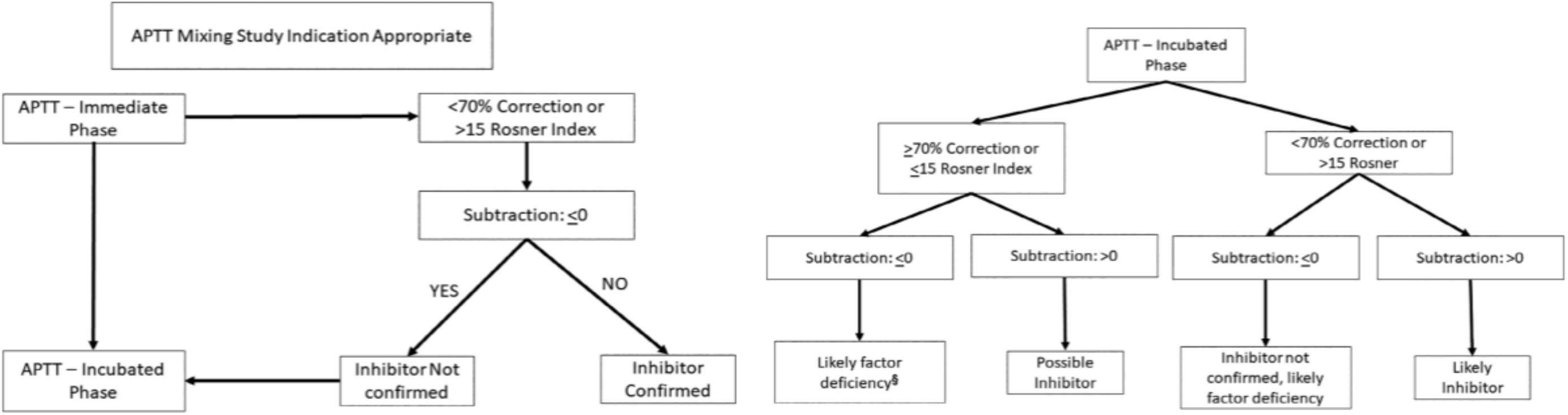


Figure 1. Recommended method for analysis based on the 2024 ICSH guidelines.

Method (units)	Formula
Percentage Correction (%) (PC)	$\frac{\text{Patient Baseline Result} - 1:1 \text{ Mix Result}}{\text{Patient Baseline Result} - \text{NPP Result}} \times 100$
Rosner Index (%) (RI)	$\frac{1:1 \text{ Mix Result} - \text{NPP Result}}{\text{Patient Baseline Result}} \times 100$
Subtraction (seconds)	1:1 Mix Result - NPP Result

Table 1. Recommended calculations based on the 2024 ICSH guidelines.

CONCLUSIONS

Application of the 2024 ICSH guidelines did not resolve diagnostic ambiguity. Subtraction analysis was unemployable since all cases were $\geq$ 0. In addition, there was no strong concordance in the method interpretation of immediate and incubated phase using the ICSH 2024 guidelines. RI>15% and PC<70% showed good sensitivity and high PPV for lupus anticoagulant but poor specificity. Neither RI $\leq$ 15% nor PC $\geq$ 70% reliably predicted factor deficiency, although multifactor deficiencies suggest non-specific interference rather than true isolated deficiency. Limitations were that not all mixing study cases proceeded with either lupus or factor testing. The guidelines also did not reflect the volatility of the APTT assay in a hospital setting as it can be affected by other nonspecific interference factors such as infection/inflammation.

REFERENCES

Adcock DM, Moore GW, Kershaw GW, S. A. L. Montalvao, Gosselin RC. International Council for Standardization in Haematology (ICSH) recommendations for the performance and interpretation of activated partial thromboplastin time and prothrombin time mixing tests. International Journal of Laboratory Hematology. 2024 Jul 15;