BRIEF REPORT

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# Evaluation of point-of-care International Normalized Ratio in sickle cell disease

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## Abstract

**Background:** Point-of-care (POC) International Normalized Ratio (INR) measurement provides efficient monitoring of warfarin therapy; however, its reliability may be affected in patients with anemia, such as those with sickle cell disease (SCD).

**Objectives:** To evaluate the correlation of POC-INR to clinical laboratory INR (CL-INR) in SCD and use of a correction factor.

**Patient/Methods:** In this retrospective study, the accuracy of POC-INR compared to CL-INR was evaluated in a cohort of patients with SCD and in a non-SCD Black cohort.

**Results:** Despite the difference in anemia, the SCD cohort showed a similar percentage of in-range POC-INR values as observed in the non-SCD cohort (37% vs 42%). The SCD cohort was randomly divided to form discovery and validation cohorts. In the discovery cohort, 86% of POC-INRs were in range when the POC-INRs were <4.0, but only 24% were in range if POC-INRs were ≥4.0. A linear regression of CL-INR versus POC-INR for POC-INR values ≥4.0 yielded a coefficient of 0.72 (95% confidence interval, 0.69-0.75); Multiplying POC-INR by this correction factor, rounded to 0.7 for ease of use in clinical practice, improved the proportion of in-range POC-INR values ≥4.0 from 24% to 100% in the SCD discovery cohort and from 19% to 95% in the SCD validation cohort. Similar findings applied to analyses of the non-SCD cohort.

**Conclusions:** POC-INR and CL-INR in patients with SCD are similar when POC-INR is <4.0, and the accuracy of POC-INR values ≥4.0 can be improved by applying an institution-specific correction factor.

**Essentials**

- The reliability of point-of-care (POC) International Normalized Ratio (INR) may be affected by anemia.
- The evidence on accuracy of POC-INR in sickle cell disease (SCD) is lacking.
- Predictability of POC-INR in SCD is high except when POC-INR values are ≥4.
- Applying a correction factor to POC-INR ≥4 in SCD improves accuracy.

# 1 | BACKGROUND

Warfarin, an oral vitamin K antagonist anticoagulant, inhibits the postsynthetic modification of several clotting factors, specifically factors II, VII, IX, and X as well as protein C/S and is indicated for the prevention and treatment of venous thrombosis and thromboembolic complications associated with atrial fibrillation and cardiac valve replacement.[1] Despite the development of newer classes of oral anticoagulants, warfarin still appears to have better adherence and is still frequently used in treating and preventing thrombosis, especially in patients with renal dysfunction.[2] With a narrow therapeutic window, warfarin use requires close monitoring to minimize bleeding and thrombosis risk.[3] Measuring prothrombin time using the International Normalized Ratio (INR) is an essential component of warfarin therapy monitoring to maintain target anticoagulation levels. Point-of-care (POC) INR testing using finger-stick blood samples offers the benefits of patient self-testing, rapid turnaround time, and reduced amount of blood required.[4] Additionally, POC-INR testing improves testing efficiency and patient satisfaction compared to traditional venipuncture methods.[5] However, factors such as anemia may affect the test accuracy of POC-INR. Two studies using the CoaguChek XS Plus or CoaguChek S system (Roche Diagnostics, Mannheim, Germany) demonstrated high reliability of POC-INR in patients with anemia,[6,7] whereas another study showed anemic patients had more out-of-range POC-INR as measured by using the Hemochron Signature Elite device (International Technidyne Corporation, Piscataway, NJ, USA).[8] The predictability of POC-INR appeared to be poor for values >3, and was improved by an institution-specific correction factor.[9]

Sickle cell disease (SCD) is a genetic disorder caused by homozygous or compound heterozygous mutations in the beta-globin gene that affects approximately 100 000 people in the United States.[10] As a hypercoagulable state, thrombosis is prevalent in patients with SCD, ranging from 3% in children to 25% in adults,[11,12] and warrants the use of anticoagulants such as warfarin. Managing warfarin use in the patient population with SCD is challenging, as only a small proportion (17%) of patients with SCD prescribed warfarin are at goal INR, generally between 2 and 3.[13] Anemia is one of the common clinical presentations in SCD, and the degree of anemia varies from mild/moderate cases in the hemoglobin SC (HbSC) or Sbeta+type (Hb 11–12 g/dL) to the severe cases in the HbSS or Sbeta0 type (Hb ~8 g/dL).[14] The reliability of POC-INR may also be affected, although evidence on the accuracy or correction of POC-INR in this patient population is lacking. This study evaluates the correlation of POC-INR to clinical laboratory INR (CL-INR) in patients with SCD and assesses the use of a correction factor to improve the accuracy of POC-INR.

# 2 | METHODS

Adult (≥18 years old) patients with SCD treated at the University of Illinois Hospital and Health Sciences System (UI Health) from 2015 to 2017 who had POC-INR and CL-INR values measured within 12 hours of the POC-INR were identified from the electronic health records. POC-INR was measured using the CoaguChek XS system (Roche Diagnostics), a Clinical Laboratory Improvement Amendments (CLIA)-waived instrument, and validation/proficiency testing is performed for all users annually. CL-INR was measured using Stago STA-R Evolution (Diagnostica Stago Inc, Parsippany–Troy Hills, NJ, USA) in a CLIA-certified lab, and the instrument is validated every 6 months with the use of new reagent lots. A total of 56 INR pairs composed of 100% Black individuals met inclusion criteria: 28 pairs were randomly selected and formed a discovery cohort; the other 28 pairs were used to form the validation cohort. The use of a validation cohort was to test the external validity of the correction factor calculated from the discovery cohort. A cohort of 1049 Black patients without SCD with POC-INR and CL-INR values measured within 12 hours who were treated at UI Health during the same time period formed the non-SCD group. In-range POC-INR was defined as a value within ±0.5 of the CL-INR when the POC-INR was <2.0 or which was ±30% of the CL-INR when the POC-INR was ≥2.0.[15] Patient demographic and clinical characteristics were recorded. Descriptive statistics, the Kruskal-Wallis test, and the chi-square test were used for data analysis. A coefficient (correction factor) was derived using POC-INR results ≥4 in the discovery cohort by forcing a linear regression through an intercept of 0 for easy use in clinical practice. POC-INR values ≥4 were adjusted by multiplying it by the correction factor. The study was approved by the Institutional Review Board (#2020-0191).

# 3 | RESULTS AND DISCUSSION

Of the 56 INR pairs in the SCD cohort meeting the inclusion criteria, all subjects were of Black ancestry. Patients with SCD were younger (38 vs 59 years) than the non-SCD cohort, and more anemic with hematocrit 27% (IQR, 24%-32%) versus 37% (IQR, 33%-42%) (Table 1). The percentage of male patients was slightly lower in the SCD cohort. The majority of the indications in the SCD cohort were due to deep vein thrombosis or pulmonary embolus.[13]

The difference between POC-INR and CL-INR was comparable in the SCD cohort and the non-SCD cohort. Thirty-seven percent of POC-INRs in the SCD cohort were within acceptable range of the CL-INR as defined in the methods, which was similar to the non-SCD cohort (42%). Only 21% of POC-INR values ≥4 in the SCD cohort were within an acceptable range. The majority (94%) of out-of-range POC-INR values were when INR was ≥4, which was also observed in the non-SCD cohort (Table 1).

The discovery and validation cohort characteristics were similar (Table 2). Since the majority of discrepancies resulted when POC-INR was ≥4, a correction factor of 0.72 was derived using a linear regression model of CL-INR versus POC-INR (95% confidence interval, 0.69–0.75; n = 21; $P<.001$, $R^2$, 0.99) with POC-INR ≥4 in the discovery cohort (Table 3). Using the same approach, a correction factor for POC-INR ≥4 in the non-SCD cohort was also calculated

**TABLE 1** SCD and non-SCD cohort comparison

| | SCD cohort (N = 56) | Non-SCD cohort (N = 1049) |
|---|---|---|
| Age, y | 38 (29-54) | 59 (49-69) |
| Black, % | 100 | 100 |
| Sex, male, % | 23 | 38 |
| Hematocrit, % | 27 (24-32) | 37 (33-42)[a] |
| POC-INR | 4.3 (3.8-5.4) | 4.3 (3.4-4.9) |
| CL-INR | 3.2 (2.6-3.8) | 3.1 (2.6-3.6) |
| INR difference | 1.2 (0.6-1.5) | 1.1 (0.6-1.5) |
| In-range POC-INR,[b] % | 37 | 42 |
| In-range values when POC-INR ≥4, % | 21 | 27 |
| Out-of-range values when POC-INR ≥4, % | 94 | 86 |

Abbreviations: CL-INR, clinical laboratory International Normalized Ratio; POC-INR, point-of-care International Normalized Ratio; SCD, sickle cell disease.

[a]From a subset of randomly selected subjects (N = 56). Median with interquartile range (IQR) was shown.

[b]In-range values are defined as an INR within ±0.5 of CL-INR when POC-INR was <2 or ±30% of CL-INR when POC-INR was ≥2.[15]

**TABLE 2** SCD discovery and validation cohort characteristics

| | Discovery cohort (N=28) | Validation cohort (N=28) | P value |
|---|---|---|---|
| Age, y | 48 (29-56) | 36 (29-51) | .43 |
| Sex, male, % | 21 | 25 | .75 |
| HgbSS genotype, % | 61 | 68 | .58 |
| POC-INR | 4.4 (3.3-5.4) | 4.2 (3.8-5.4) | .71 |
| CL-INR | 3.2 (2.3-3.8) | 3.1 (2.6-3.6) | .81 |
| INR difference | 1.3 (0.7-1.6) | 1.1 (0.6-1.5) | .47 |
| Hematocrit, % | 27% (25-34%) | 28% (24-35%) | .73 |

Abbreviations: CL-INR, clinical laboratory International Normalized Ratio; POC-INR, point-of-care International Normalized Ratio; SCD, sickle cell disease.

**TABLE 3** Correction factor comparison in subjects with POC-INR ≥4

| POC-INR samples | SCD (N = 21) | Non-SCD (N = 722) |
|---|---|---|
| Coefficient (95% CI) | 0.72 (0.69-0.75) | 0.72 (0.71-0.73) |
| P value | <.001 | <.001 |
| $R^2$ | 0.99 | 0.98 |

Note: A coefficient (correction factor) was calculated using POC-INR results ≥4 by forcing a linear regression through an intercept of 0 for easy use in clinical practice.

Abbreviations: CI, confidence interval; POC-INR, point-of-care International Normalized Ratio; SCD, sickle cell disease.

factor for POC-INR ≥4 should be derived and applied similarly to improve the predictability of POC-INR in both patients with and patients without SCD. To our knowledge, this is the first study assessing the correlation and correction of POC-INR in patients with SCD. Despite the convenience that POC-INR measures provide, the test accuracy may be affected in patients with anemia, and studies using different POC-INR instruments show conflicting results.[6-8] In the present study of patients with SCD, we found the correlation of POC-INR and CL-INR was 86% when POC-INR was <4 (Table 4), but the agreement of POC-INR decreased to 21% when POC-INR was ≥4 (Table 1). These findings were not specific to patients with SCD or to the POC-INR instrument used here. Applying a correction factor to POC-INR increases the agreement with CL-INR and provides benefits of cost savings and expedited results without the need of repeating CL-INR for above-average POC-INR. However, the accuracy of POC-INR appears to be still low even after adjustments for those POC-INR >7 as shown in Figure 1, and confirmatory CL-INR may be necessary to mitigate the potential bleeding risk.

Our study has several limitations. First, this was a single-center retrospective study, and the results may not apply to other institutions using different POC-INR devices, although the decreased accuracy in elevated POC-INR and a similar correction factor have been reported in another study.[9] Thus, institution-specific correction factors may need to be derived for elevated POC-INR. Second, POC-INR values ≥4 must be repeated with CL-INR per our institution's anticoagulation management protocol, which resulted in the observed uneven distribution of POC-INR values <4 and ≥4 in our study and may introduce possible selection/sampling bias. Third, our study had a relatively small sample size, and caution should be exercised when interpreting the results. Fourth, there may be patients with similarly elevated POC-INR who did not have the CL-INR measured and may have different characteristics than those who were included.

In conclusion, agreement between POC-INR and CL-INR in patients with SCD is high except when POC-INR values are ≥4. Similar to patients without SCD, application of an institution-specific correction factor to POC-INR with value ≥4 improved POC-INR accuracy in this patient population.

as 0.72 (Table 3), identical to the correction factor derived from the patients with SCD. Applying the correction factor, rounded to 0.7 for easy use in clinical practice, significantly improved in-range POC-INR from 24% to 100% in the discovery cohort (P<.001) (Table 4). In the validation cohort, in-range POC-INR improved from 19% to 95% (P<.001) after applying the correction factor of 0.7 (Table 4; Figure 1).

Our results demonstrated that POC-INR tends to overestimate a simultaneous CL-INR when POC-INR is ≥4 in patients with SCD, and a correction factor significantly improved POC-INR agreement with CL-INR. Despite the difference in anemia, the accuracy of POC-INR and correction factor were similar between patients with and without SCD, suggesting that an institution-specific correction

| | POC-INR within acceptable CL-INR range | | P value |
| --- | --- | --- | --- |
| | Unadjusted | Adjusted | |
| Discovery cohort | | | |
| All, N = 28, n (%) | 11 (39) | 27 (96) | <.001 |
| POC-INR <4, N = 7, n (%) | 6 (86) | NA | NA |
| POC-INR ≥4, N = 21, n (%) | 5 (24) | 21 (100) | <.001 |
| Validation cohort | | | |
| All, N = 28, n (%) | 10 (36) | 26 (93) | <.001 |
| POC-INR <4, N = 7 | 6 (86) | NA | NA |
| POC-INR ≥4, N = 21 | 4 (19) | 20 (95) | <0.001 |

**TABLE 4** Unadjusted and adjusted POC-INR in the discovery and validation SCD cohorts

*Note:* Adjusted value =unadjusted × 0.7 when POC-INR ≥4. Acceptable POC-INR range: INR difference within ±0.5 of CL-INR when POC-INR <2 or ±30% of the CL-INR when POC-INR ≥2.

Abbreviations: CL-INR, clinical laboratory International Normalized Ratio; NA, not applicable; POC-INR, point-of-care International Normalized Ratio; SCD, sickle cell disease.
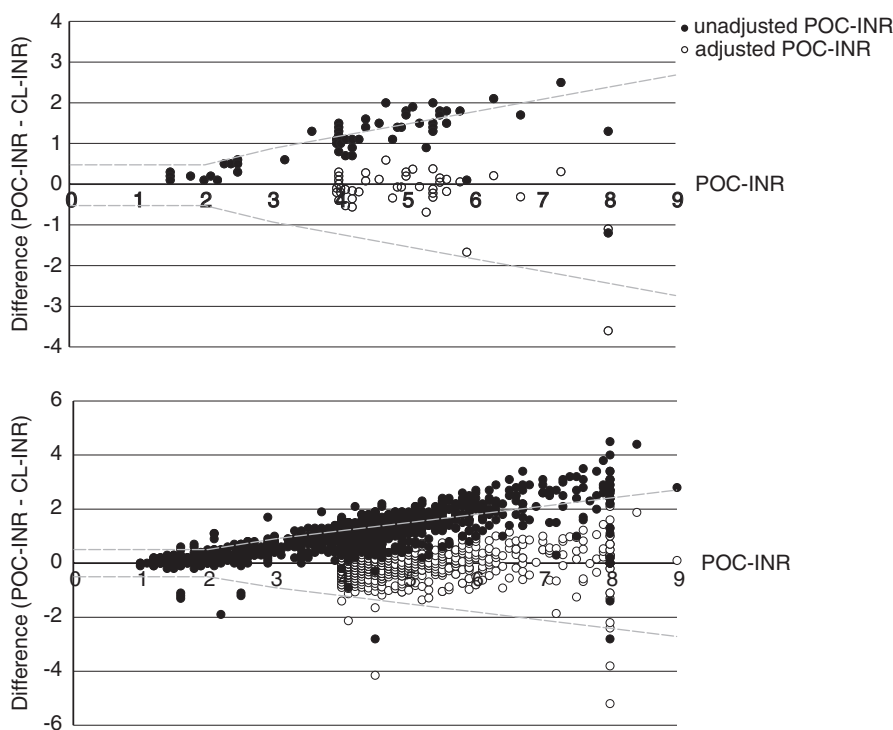


**FIGURE 1** Unadjusted and adjusted POC-INR in SCD and non-SCD cohorts. POC-INR in the discovery and validation cohorts combined (top panel) and non-SCD cohort (bottom panel). Unadjusted POC-INRs are represented by black dots. POC-INRs ≥4 were adjusted by multiplying the correction factor of 0.7 and are represented by white dots. The acceptable POC-INR range, defined as measurements within ±0.5 of the CL-INR when the POC-INR <2.0 or ±30% of the CL-INR when the POC-INR ≥2, is shown using dashed lines. CL-INR, clinical laboratory International Normalized Ratio; POC-INR, point-of-care International Normalized Ratio; SCD, sickle cell disease

## RELATIONSHIP DISCLOSURE

The authors declare no conflicts of interest.

## AUTHOR CONTRIBUTIONS

JH, EAN, SLS, and VRG designed research, analyzed the data, and wrote the paper. SR and AS performed research. REM, MG, FN, FAH, and JL analyzed the data and wrote the paper.

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