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REVIEW
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Hemoglobin clinical decision limits: Chasing the numbers

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ABSTRACT

Background: The interpretation of hemoglobin (Hb) values in clinical practice involves both absolute thresholds and relative changes, yet alignment between clinical decision limits (CDLs) and laboratory quality control (QC) thresholds is unclear. This study aimed to compare published CDLs for Hb used in diagnosis and treatment with those applied in laboratory internal QC processes.

Methods: A literature search was conducted in PubMed (2018–2023) targeting adult populations. Eligible studies reported specific Hb thresholds or clinically relevant changes; case reports, case-control studies, and papers lacking these data were excluded.

Results: Out of 507 initial articles, 131 met eligibility criteria. Among these, 121 referenced significant changes in Hb values, with a mean change of 1.08 g/dL (range: 0.50–3.50 g/dL). The most frequently cited clinically meaningful change was 2.00 g/dL. Conversely, changes under 0.40 g/dL (mean 0.39 g/dL) were generally considered clinically insignificant. Transfusion thresholds were consistently reported at 7.00–8.00 g/dL. Values of 10.00, 11.50, 12.00, and 13.00 g/dL were cited across studies involving CKD hemodialysed and non-hemodialysed patients, anemia, or patient stratification.

Conclusions: There is substantial heterogeneity in reported Hb CDLs across clinical contexts. Current QC thresholds may overlook variations important to clinicians. Harmonizing QC strategies with clinical practice could enhance measurement reliability and patient care.

Keywords: biological variation, clinical decision-making, hemoglobin, quality control, laboratory

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INTRODUCTION

Interpretation of laboratory test results by physicians is a complex and nuanced process. The way a physician interprets a single value, a series of values, or a change (difference) in a specific parameter cannot be reduced to a simple IF/THEN algorithm. The clinical decision process integrates laboratory data with patient history, physical examination, and clinical findings. This process is further influenced by guidelines, institutional protocols, and the individual experience of the physician [1–3].

Establishing a direct link between laboratory parameters and clinical decisions is particularly challenging and rarely linear. For certain laboratory tests, clinical decision limits (CDLs) are defined through collaboration between laboratory specialists and clinicians [4]. Although CDLs are predominantly applied in clinical settings, they are also critical for laboratory activities, especially in designing quality control (QC) strategies [5]. The ISO 15189:2022 standard recommends that the target values for internal QC materials be aligned with relevant CDLs [6]. However, few CDLs have been formally published [7,8], and it remains uncertain whether clinicians and laboratories rely on the same thresholds.

Hemoglobin (Hb) is one of the most commonly measured analytes as part of the complete blood count (CBC). Its levels are routinely used for diagnosing anemia, managing transfusion decisions, assessing therapeutic response, and monitoring conditions such as beta-thalassemia. In some studies, Hb values are also used to predict clinical outcomes. The World Health Organization (WHO) has defined threshold values for anemia diagnosis [9], which may be interpreted as CDLs, although they are not universally adopted by clinicians.

The aim of this study was to compare published clinical hemoglobin CDLs and thresholds of interest (as used in diagnosis and treatment) with laboratory CDLs used for internal quality control purposes.

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METHODS

Ethics approval was not required for this study.

An extensive literature search was conducted in the PubMed database to identify papers that listed or referenced clinical decision limits based on hemoglobin values. The search strategy included terms such as "hemoglobin values", "hemoglobin levels", and "hemoglobin intervals", while excluding terms irrelevant to the review scope, such as "glycated", "non-invasive", "point of care", and "reference values". The full search query is shown below:

((((((hemoglobin values) OR (hemoglobin levels)) OR (hemoglobin intervals)) NOT (glycated)) NOT (smartphone)) NOT (non-invasive)) NOT (outcome) NOT (reference values) NOT (reference interval) NOT (point of care)

Additional inclusion criteria were: publication between 2018-2023, adult population, and relevance to diagnosis or treatment decisions based on Hb values. Papers were eligible if they reported either specific Hb values (absolute limits) or clinically relevant changes in Hb (relative difference). Case reports, case-control studies, and articles that did not mention specific Hb thresholds or changes were excluded.

RESULTS

Of the 507 papers retrieved through the initial search, 131 met the eligibility criteria and were included in the final analysis.

Out of the 131 articles, 121 referenced clinically relevant changes in Hb values, rather than static thresholds. The mean change considered clinically significant was 1.08 g/dL, with a range of 0.5 to 3.5 g/dL. The most frequently cited significant change was 2.0 g/dL [10-27, 36-39, 41-44, 49-59, 62-95, 122-141].

A change of 0.3 g/dL was the most commonly reported as a clinically non-significant variation. The mean non-significant change was 0.39 g/dL [28-35, 43,48, 96-100], although some studies reported non-significant variations up to 1.5 g/dL.

In addition to absolute changes, a few studies reported percentage-based changes, with clinically meaningful variations expressed as relative changes in hemoglobin ranging from 2.3% to 21.0%, depending on context [36, 122, 137].

A total of 10 studies addressed Hb thresholds for transfusion decisions, as indicated by title or full text [25, 39, 44-48, 62, 96, 140]. The 7.0 or 8.0 g/dL thresholds were defined as the decision point for initiating transfusion.

DISCUSSION

Two distinct types of clinical decision limits (CDLs) were identified in the literature:

1. Absolute thresholds for diagnosis, transfusion, or therapy.
2. Relative changes in hemoglobin over time.

Many publications referenced both — clinical action could be triggered either when a fixed Hb value is reached or when a defined change is observed.

Absolute thresholds and variations across populations

Values of 10.0, 11.5, 12.0, and 13.0 g/dL were cited across studies involving CKD hemodialysed [30, 32-34, 65, 84, 95, 117] and non-hemodialysed patients [12, 13, 115], anemia [10-36], or patient stratification. Other papers referenced thresholds such as 7.0 g/dL [45, 47], 8.0 g/dL [46, 48], or 16.5 g/dL [66] depending on the population.

Relative changes in hemoglobin and their clinical significance

Change thresholds were equally variable. Some studies reported that changes as small as 0.02–0.40 g/dL were not clinically relevant [28-35, 43, 48, 67, 96-100], while others considered changes of 0.5, 1.5, or 2.0 g/dL to be significant [10-27, 36-39, 41-44, 49-59, 62-95, 122-141]. In some safety studies, percentage changes of 2.3% [122] or 5.0% [137] were considered clinically meaningful, while 21.0% was reported in a study about the risk of sudden death [36]. Interestingly, differences of 0.9 g/dL were not significant in studies about supplementation either for group B vitamins [121]. In studies about iron supplementation, values of 0.2 g/dL in pregnant women [112] were not seen as significant, while in other studies, the values of 0.26 g/dL [97] or 0.4 g/dL [51] were significant [97]. This underscores the lack of harmonization between published thresholds.

Changes in Hb values under 0.04 g/dL [30, 32] were not seen as clinically significant in randomised controlled trials. However, a change of 1.5 g/dL was both seen as not significant in a phase III trial [33] while another considered a 0.5 g/dL difference as clinically relevant [84] in treating anemia in CKD-patients.

Alignment between laboratory and clinical interpretation

From the laboratory's perspective, variations near the SD of QC materials (eg, 0.17 g/dL at 12 g/dL Hb) fall within method variability and are not flagged as significant. However, clinicians may act on these changes, particularly when they exceed 0.3–0.5 g/dL. A 0.5 g/dL shift represents a 4.2% change—below the total allowable error

(TEa) of 5.8% [142], but often cited as meaningful. This illustrates the risk of misalignment between laboratory-defined method limits and clinically interpreted thresholds.

Further examination of the literature revealed wide heterogeneity in what constitutes a clinically significant hemoglobin change. The interpretation of Hb changes as clinically significant appeared strongly dependent on context and purpose. Reported variations over 0.5 g/dL were considered relevant in treatment response, anemia correction, and post-operative monitoring. The most frequently cited significant change, especially in settings involving transfusion thresholds or anemia recovery, was 2.0 g/dL. Notably, a 0.5 g/dL change was repeatedly mentioned in randomized controlled trials as a marker for treatment efficacy or risk stratification.

Conversely, changes around 0.3 g/dL or lower were generally interpreted as not clinically actionable. This suggests a grey zone between 0.3–0.5 g/dL, where interpretation depends heavily on clinical context. These limits are shown in Figure 1.

These values overlap with typical QC standard deviations. For example, a QC material with a mean of 12.0 g/dL and SD of 0.17 g/dL implies that a 0.3–0.5 g/dL change lies within 2–3 SDs—often dismissed as acceptable method variation by laboratory professionals. This reinforces the idea that QC systems are not always designed to detect changes that are clinically meaningful, particularly at the thresholds used for transfusion or treatment adjustment.

Reference Change Value

In such borderline situations, the Reference Change Value (RCV) may serve as a useful tool to support interpretation. By addressing both analytical and biological variation [143], RCV can help assess whether small hemoglobin changes, such as those within the 0.02–0.4 g/dL range or the 0.3–0.5 g/dL grey zone, are likely to represent true physiological shifts rather than expected fluctuation.

To bridge this gap between analytical interpretation and clinical significance, the development of a prospective study is needed. Such a study could: (1) survey clinicians from multiple specialties (eg, nephrology, surgery, hematology) to document the hemoglobin thresholds they apply in practice, (2) collect parallel input from laboratory professionals on how these changes are interpreted analytically, and (3) evaluate the consistency between actionable thresholds and established QC/MDL practices. The outcome could inform guidelines on aligning clinical decisions with laboratory performance standards, ultimately improving both test interpretation and patient safety.

Table 1. Summary of medical decision limits and hemoglobin changes by their clinical relevance

Clinical Context	Reported Hb Values (g/dL)	Notes
Transfusion threshold (surgical/critical care)	7.00 – 8.00	Common threshold; associated with outcomes and transfusion decision-making
WHO non-anemia threshold	12.00 – 13.00	Used in QC planning; also referenced as a clinical threshold
WHO anemia diagnosis range	7.00 – 12.90	Broad range depending on sex and context
CKD-related treatment threshold	10.90 – 13.00	Used in anemia management and CKD trials
High-end threshold (rarely used)	16.50	Rarely cited; found in one study [66]
Clinically significant Hb change (response to treatment)	0.50 – 3.50	Varies across studies and conditions
Clinically non-significant Hb change	0.02 – 0.40	Typically considered within analytical variation

Abbreviations: CKD- chronic kidney disease, Hb- hemoglobin, QC- quality control, WHO- World Health Organisation.

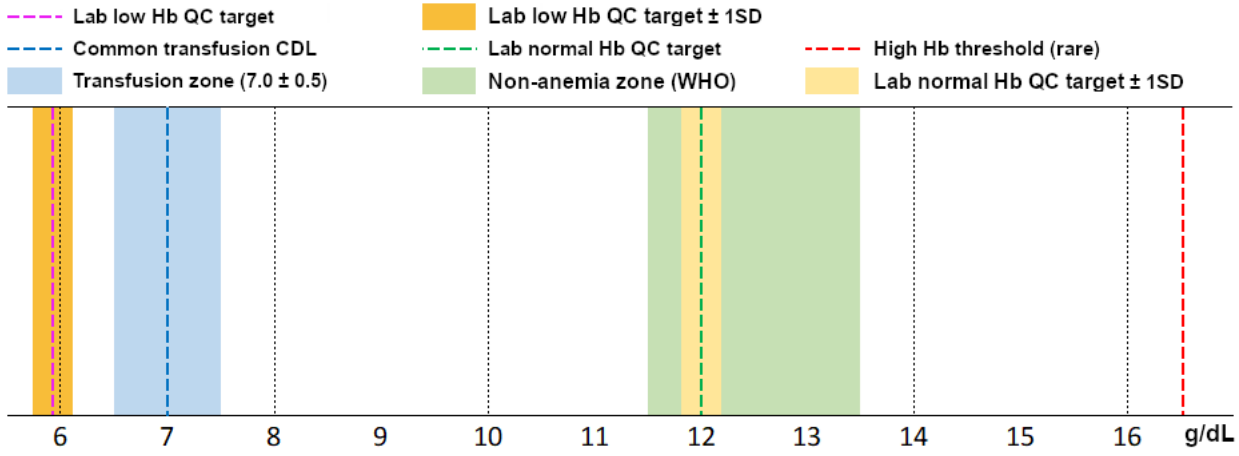

Figure 1. Laboratory QC targets from our laboratory data (low, normal, high) and their SDs are illustrated. Transfusion CDL is illustrated at 7.0 g/dL according to data found in the papers included in the analysis. WHO non-anemia zone is illustrated according to the published thresholds.

Study limitations

Several limitations should be acknowledged, mainly because it was not designed as a systematic review. The study has the risk of bias as the literature search was performed only in PubMed database and not all possible search terms were used for the query. The high heterogeneity of data might be explained by the high number of different medical areas. We found only one study that specifies high threshold values for Hb but this may be explained by the fact that polyglobulia is much rarer than anemia.

CONCLUSIONS

The analysis reveals substantial heterogeneity in the hemoglobin thresholds used across clinical studies. CDLs range widely depending on clinical context. Changes similar to the SD of QC materials are typically regarded as methodological noise in the lab, yet may influence medical decisions. Laboratories should therefore critically evaluate whether their MDLs reflect clinically actionable change and adapt their QC strategy accordingly.

ABBREVIATIONS

CBC – complete blood count

CDL – clinical decision limit

Hb – hemoglobin

ISO – International Organization for Standardization

QC – quality control

RCV – Reference Change Value

SD – standard deviation

TEa – Total Allowable Error

WHO – World Health Organization

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AUTHORS' CONTRIBUTION

ORO: conceptualization, data curation, methodology, writing – original draft, writing – review and editing, supervision

ECP: conceptualization, data curation, writing – original draft.

All authors have read and approved the final version of the manuscript.

CONFLICT OF INTEREST

None to declare.

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