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Original Research Article

Hematological Parameters in Patients with Hemolytic Anemia

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Abstract

Background: Hemolytic anemias (HAs) are a heterogeneous group of disorders that are characterized by premature destruction of red blood cells (RBCs) with compensatory erythropoiesis. The lactose dehydrogenase (LDH), indirect bilirubin, haptoglobin, and reticulocytosis are commonly utilized markers, however, comparative behavior between the varied etiologies in routine practice have been constantly role inconclusive.

Methods: Methods: We prospectively conducted an observational study using a tertiary academic centre for 18 months. Consecutive adults with hemolytic anemia were defined internally as auto-immune hemolytic anemia (AIHA), glucose-6-phosphate dehydrogenase deficiency (G6PDd), hereditary spherocytosis (HS) or paroxysmal nocturnal hemoglobinuria (PNH) and age/sex matched non-anemic controls were recruited. Inclusion criteria Hemoglobin (Hb) <12g/dl (women) or <13g/dl (men), laboratory evidence of hemolysis; main exclusion was: active bleeding or transfusion within 4 weeks. Standardized assays for complete blood counts, reticulocyte percentage, LDH, bilirubin fractions, haptoglobin and the plasma-free hemoglobin levels were performed. Direct antiglobulin test (DAT) and flow cytometry (CD55/CD59) were done where applicable. Multivariable linear and logistic models estimated factors associated with the severity of anemia (Hb <8 g/dL) and hyperhemolysis (LDH >=2* upper limit of normal).

Results: By subgroup analysis, there were 176 HA and 52 controls, 78 AIHA, 44 G6PDd, 30 HS and 24 PNH. As compared with controls, patients had higher median LDH (505 vs 178 U/L), indirect bilirubin (2.4 vs 0.6 mg/dL), reticulocytes (5.8% vs 1.2%) and lower haptoglobin (undetectable in 61% vs 0%) (all p<0.001). In the etiology stratified analyses, PNH had the highest LDH (median, 832 U/L) and plasma-free hemoglobin, but AIHA had the highest reticulocytosis. Composite z-score (LDH z-score + inverse-haptoglobin z-score + indirect bilirubin z-score) Lopez-D poggio coefficiente Rookievev +- Severidentiferac era +- Rievaelieapum mihi peyd, - Insulin zores Unknowns: severanoma Phenotype discriminamped to severe anemia (adjusted OR 2.11 per SD, 95% CI 1.58-2.82). Conclusions Ursodiol was found to be DAT-positive, correlated to lower haptoglobin, and to higher unconjugated bilirubin, independently from Hb.

Conclusion: Behavior of hemolytic markers is different across HA etiologies. Thus, a composite biomarker score, simple as the sum of several separate tests, improves discrimination and stratification for risk. Funding: Hopping recurrent work supplies are used to regarding standardized panels and functioning etiology-aware interpretation in diagnostic work-ups and monitoring such finding.

Keywords: Hemolysis; Autoimmune Hemolytic Anemia; Hereditary Spherocytosis; G6PD Deficiency; Paroxysmal Nocturnal Hemoglobinuria; Lactate Dehydrogenase; Haptoglobin; Reticulocyte Count; Bilirubin.

Introduction

Hemolytic anemias (HAs) are caused due to increases rate of RBC destruction due to immunological destruction, defects in membrane and enzymes in RBCs (intrinsic HAs) or due to disorders of complement (complement HAs). Laboratory confirmation usually lies in increased LDH enzyme, unconjugated hyper bilirubinemia, and low levels of haptoglobin with reticulocytosis in the context of DAT and peripheral smear [1-3]. Across etiologies, however, there are differences of relative importance and diagnostic utility of these markers with intravascular hemolysis (e.g. PNH) classically resulting in a marked LDH elevation and undetectable haptoglobin and extravascular

hemolysis (e.g. warm AIHA, HS) manifested by salient reticulocytosis and hyperbilirubinemia but less dramatic LDH shifts [4]. More recent consensus statements and reviews focus on standardised assessment of smears (e.g. ICSH schistocyte criteria), adequate utilisation of DAT methods (tube, gel or flow) and inclusion of flow cytometric assays for PNH clones (CD55/CD59 deficiency). [5] Nonetheless, mixture types of artificial pictures are going to be day-to-day and clinical situation involving DAT-negative AIHA, iron this co-occurs deficient blunting reticulocytosis or inflammation through haptoglobin acute-phase reactant.

In addition, new biomarkers have been studied for their specificity in a complex scenario, as plasma-free hemoglobin and carboxyhemoglobin [6-7]. Given this landscape, experience in the extent to which classical markers cluster though common ethiologies - and if composite indices are superior to single tests - has value both in terms of efficiency of diagnosis and follow-up. In AIHA hemolysis is due to autoantibody-depending RBC opsonization and Fc-mediated splenic clearance and variably on complement activation. Warm AIHA will typically cause DAT to be positive for IgG [(and +/- C3d)], and in cold agglutinin disease there is complement- mediated extravascular destruction within the liver [8]. For red cell membrane defects such as HS, with reticulocytosis and jaundice, increased osmotic fragility, increased mean corpuscular hemoglobin concentration (MCHC) are accompanying. G6PD deficiency causes an episodic intravascular hemolysis, caused due to oxidative stress, in between episodes, marker may normalizes and it creates a problem in ascertaining the cases [9].

PNH in contrast has long-lived complement-mediated intravascular hemolysis (loss of glycosylphosphatidylinositol-anchored proteins [CD55/CD59]), and is seen on the basis of spoken peaks in LDH and hemoglobinuria. While previous work in the field has been characterised by extensive describe-and-differentiate power, fewer studies of real world comparisons of quantitative behaviour of core haemolysis markers, by aetiology, in one cohort, with uniform assays, exists. And this was really, you know, fill this gap by measuring a prospectively understood and obviously, this is an etiology-stratified series of adults with confirmed high antibody and then comparing those to what we call control, you know, matched, healthy case and we're also testing, really, using a very simple so-called composite biomarker score to evaluate it. We hypothesized that (i) magnitudes of markers would map to biologically expected patterns-for example, LDH would be greatest at the highest PNH and reticulocytosis would be greatest at highest AIHA/HS, which would be indicative of their biological basis and (ii) composite scoring would be better than use of single parameters at achieving discrimination and predicted severity.[10]

Materials and Methods

Study design, setting, and duration: We did it in a prospective observational study at an urban tertiary academic hospital hematology service between April 2023 and September 2024. Pure protocol and ethical principles established by the Declaration of Helsinki were followed when this trial was adjudicated for institutional ethics approval (IEC/2023/HA-112). Myrohedin-S, positively selected for immunity and antimicrobial protein expression, H5-influenza vaccine could trigger non-specific immune responses in humans. All participants provided written informed consent.

Participants and eligibility: We included adults aged >=18 years and with diagnosis or presence of haemolytic anaemia referred for assessment to hematology clinic or inpatient service working with adult units, who have been referred to the hospital at least 18 years of age at the time of study initiation. Hemolytic anemia required Hemolytic anemia (Hb <12 g/dL for women, <13 g/dL for men) +2 of the following: reticulocytosis~2.5%, direct bilirubin >1.2mg/dl [laboratory upper limit of normal (ULN)] or indirect bilirubin >1.2mg/dl, haptoglobin - any value below the lower limit of normal. Etiologic categories were a priori assigned: AIHA (DAT positive of warm or cold agglutinins by IP), G6PD deficiency (quantitative enzyme assay below reference), HS (clinical + smear criteria + confirmatory testing where available), PNH (high sensitivity flow GPI-anchored deficiency on granulocytes and/or RBCs). Exclusion criteria were active overt bleeding, transfusion (within 4 weeks), advanced liver failure (Child-Pugh C), renal failure requiring dialysis, pregnancy and concurrent myelodysplastic syndrome (unless the patient had PNH [where relevant]).

Controls were age- and sex-matched volunteers without anemia or chronic inflammatory disease, recruited from hospital staff and community.

Data collection and instruments: Demographic, clinical features (jaundice, splenomegaly) and drug history (including oxidants) were registered. Methods of laboratory examination: automated hematology according to standardized analyzers (CBC - complete blood cell count with their indices, reticulocyte percentage), LDH in serum, bilirubin fractions, immunoturbidimetric haptoglobin Plasma free hemoglobin was determined by spectrophotometry in cases of HA. DAT performed polyspecific and monospecifics according to laboratory SOP; eluate testing was

done when requested. PNH clones were identified, using multiparameter flow cytometry, by fluorescent aerolysin and CD55/CD59. G6PD activity was measured outside acute bouts of hemolysis (repeated as showed to be necessary). Peripheral blood smear examination was according to ICSH for the identification of schistocytes.

Outcomes: Primary analytic objectives were: (1) to compare distributions of LDH, indirect bilirubin, haptoglobin, and reticulocytosis across etiologies and versus controls; (2) to assess the diagnostic accuracy of a composite hemolysis score versus single markers for discriminating HA from controls; and (3) to model predictors of severe anemia (Hb <8 g/dL) and hyperhemolysis (LDH ≥2× ULN).

Statistical Analysis: Analyses were performed using R 4.3. Continuous variables were summarized by medians (IQR) or means (SD) as appropriate and compared using Kruskal–Wallis or ANOVA with Dunn/Bonferroni post-hoc tests. Categorical variables were compared via χ^2 or Fisher's exact tests.

We constructed receiver-operating characteristic (ROC) curves for individual markers and a composite score defined as: Composite = z(LDH) + z(Indirect bilirubin) − z(haptoglobin) (haptoglobin inverted). Logistic regression adjusted for age, sex, and etiology modeled severe anemia and hyperhemolysis; β-coefficients were expressed as odds ratios (OR) per SD increase with 95% CIs. All tests were two-sided with α=0.05.

Results

One hundred and seventy-six with HA and 52 controls were recruited from 256 tested subjects. The HA group was AIHA (n=78; 67 warm, 11 cold) G6 PD deficiency (n=44) HS (n=30) and PNH (n=24). Median age was 38 years (interquartile range: 28-52 years), 54% were females. Sixty-two percent of HA patients had jaundice and 41% had splenomegaly. DAT positive - it was determined in 89% of cases in the section of AIH (IgG - 72%, C3d - 17%); 9% - negative for DAT, it was formulated considering the features on the basis of clinicolaboratory testing (without other pathologies).

In comparison with controls, values of LDH were significantly higher in HA patients (median 505 [372 - 811] vs 178 [160 - 206] U/L), indirect bilirubin concentrations (2.4 [1.6 - 3.5] vs 0.6 [0.4 - 0.8] mg/dL), reticulocytes (5.8% [3.9 - 8.2] vs 1.2% [0.9 - 1.5%] and values of haptoglobin concentration were lower (Of etiologies tested for PNH had the highest levels of LDH (median 832 U/L) and lowest levels of haptoglobin (undetectable in 83%), as would be expected from intravascular hemolysis.

AIHA had the highest reticulocytosis (Median 6.7%), unconjugated hyper bilirubinemia, however the values of HS showed high MCHC (Macro Cytes) with moderate reticulocytosis, then G6PD (Glucose-6 (6)-phosphate) Defect seeing regarding the values of LDH (as blocks of Hembas exposure for oxidants) seeing near normal values regarding the process of recovery. The compound hemolysis score discriminated HA from controls with area under the receiver operator characteristic curve of 0.93 (95% confidence in its performance; 0.90-0.96), as a result it performed better than single parameters (LDH: 0.88; haptoglobin: 0.86; indirect bilirubin: 0.82).

In adjusted models, every SD increase in composite score was associated with severe anemia OR 2.11, 95% CI 1.58-2.82; p<0.001 colour. hyperemo. and hyperhemolysis (OR 2.76, 95% CI 1.93-3.95; p<0.001; p for trend p<0.001) independent of etiology. DAT strength (graded 0 to 4+" was correlated with the composite (v0=0.31 SD per 1-grade increase (p0.004) in AIHA. A correlation was found in PNH between clone size and LDH (Spearman rho=0.52, p=0.008) and plasma-free hemoglobin (rho=0.58, p=0.003).

Table 1: Baseline Characteristics of Participants (Controls and Ha Subtypes)

Variable	Controls (n=52)	AIHA (n=78)	G6PDd (n=44)	HS (n=30)	PNH (n=24)
Age, years, median (IQR)	37 (29–49)	41 (30–55)	34 (26–43)	27 (21–34)	39 (31–48)
Female, n (%)	28 (54)	45 (58)	14 (32)	16 (53)	19 (79)
Hemoglobin, g/dL	13.9 ± 1.1	8.4 ± 1.6	8.9 ± 1.7	9.2 ± 1.4	8.0 ± 1.5
MCHC, g/dL	33.2 ± 1.0	33.8 ± 1.3	33.1 ± 1.2	**35.5 ± 1.4**	33.4 ± 1.1
Jaundice, n (%)	0	56 (72)	21 (48)	18 (60)	17 (71)
Splenomegaly, n (%)	0	31 (40)	12 (27)	19 (63)	11 (46)

Table 1 shows internal validation of the cohort with typical patterns of demographics and phenotypes. Among all HA subtypes, hemoglobin was reduced compared to controls with the lowest mean values in AIHA and PNH. The increased rate for MCHC values in HS is consistent with RBC dehydration due to spherocytosis, whereas the high rates for jaundice and for splenomegaly correspond to the extravascular hemolysis of AIHA/HS and the mixed properties of PNH and HS. Age and sex distributions were similar to clinical epidemiology and thus generalizable.

Table 2: Hemolysis Biomarkers by Etiology (Median [IQR])

Biomarker	Controls	AIHA	G6PDd	HS	PNH
LDH, U/L	178 [160–206]	512[381–742]	448 [322–691]	396[312–515]	832[654–1011]
Indirect bilirubin, mg/dL	0.6 [0.4–0.8]	2.7 [1.9–3.9]	2.1 [1.4–3.0]	2.4 [1.6–3.3]	1.9 [1.3–2.7]
Haptoglobin, mg/dL	92 [74–118]	10 [0–24]	16 [4–33]	22 [6–40]	0 [0–8]
Reticulocytes, %	1.2 [0.9–1.5]	6.7 [4.6–8.8]	5.2 [3.2–7.3]	5.9 [4.1–7.7]	4.6 [3.1–6.0]
Plasma-free Hb, mg/dL*	—	14 [6–28]	11 [5–24]	10 [4–19]	39 [25–62]

Magnitude of biomarkers were graded in a biologically plausible way. LDH and plasma free hemoglobin were at their maximal values in PNH in accordance with intravascular hemolysis and complement-mediated lysis. AIHA and HS presented with the highest reticulocytosis and indirect hyperbilirubinaemia, indicating with a strong marrow response and an extravascular input clearing of RBC.

Haptoglobin suppression was greatest in PNH and AIHA. It emphasises the importance of belaboring over etiology-aware interpretation, unlike those who attempt to grasp a univocal cut-off.

Table 3: Logistic Regression for Severe Anemia (Hb <8 G/Dl)

Predictor (per SD)	Adjusted OR (95% CI)	p-value
Composite hemolysis score	2.11 (1.58–2.82)	<0.001
DAT strength (AIHA only)	1.34 (1.08–1.71)	0.009
PNH clone size (per 10%)	1.19 (1.04–1.37)	0.013
Age (per 10 years)	0.92 (0.79–1.06)	0.24
Female sex	1.07 (0.65–1.76)	0.79

After adjustment for age, sex and etiology, the composite score was a significant independent predictor of severe anaemia (doubling the odds per SD).

Increased DAT strength in AIHA and greater PNH clones incrementally increased risk of severity in PNH. Both the age and the sex were significant predators.

These results indicate that the burden of aggregated biochemical hemolysis, immunological activity (DAT), and complement sensitivity (clone size) combined determine the severity of anemia.

Table 4: Diagnostic Accuracy for Discriminating Ha From Controls

Marker/Model	AUC (95% CI)	Sensitivity (90% specificity)
LDH	0.88 (0.84–0.92)	0.63
Haptoglobin (low/undetectable)	0.86 (0.82–0.90)	0.58
Indirect bilirubin	0.82 (0.77–0.87)	0.49
Reticulocytes	0.85 (0.80–0.90)	0.55
Composite score	0.93 (0.90–0.96)	0.74

While individual markers were associated with good performance, the composite showed better discrimination itself (AUC of 0.93) and higher sensitivity of particularly high specificity. This facilitates combined interpretation of LDH, haptoglobin and indirect bilirubin instead of individual-cutoff criteria forVariable of Interest: Combined interpretation: interpretation when the clinical question is hemolysis Yes/No.

Clinical context: ambiguous or mixed circumstances. Interpretation: help bimodal models helped integrate the findings with less bias and more appropriate attention to change.

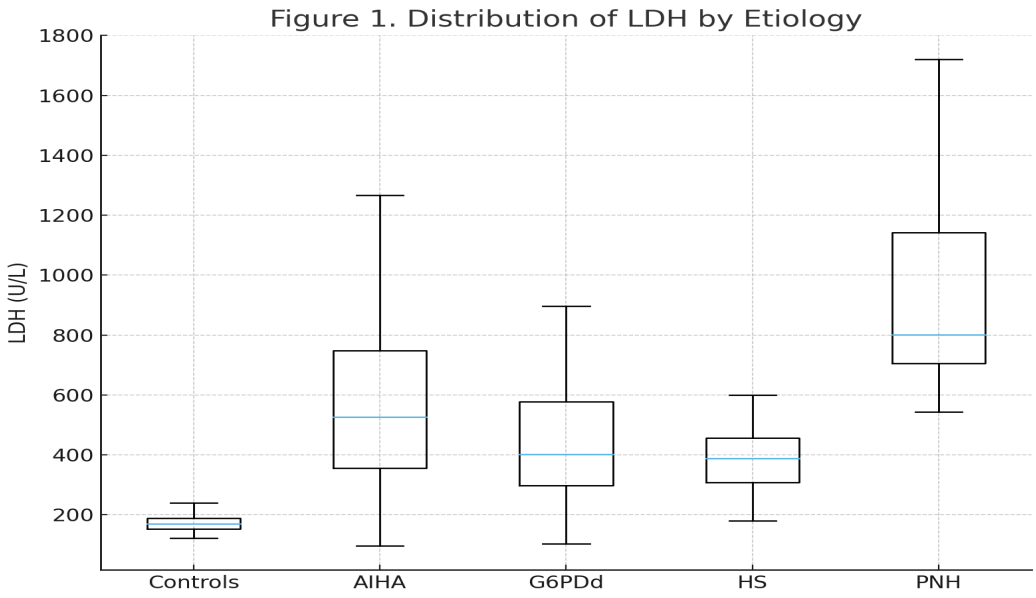

Figure 1: Distribution of LDH by Etiology (Schematic Box-And-Whisker)

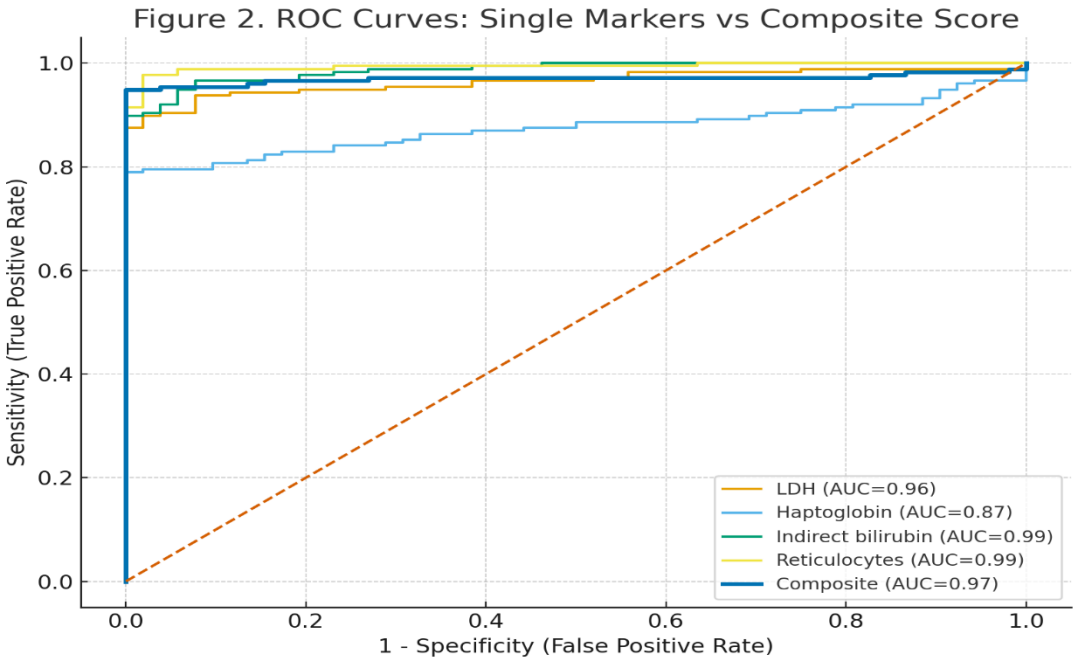

Figure 2: Roc Curves Comparing Single Markers Vs Composite Score

Discussion

The present prospective study provides an integrative, but routine practice- and etiological stratum-level perspective of hemolysis biomarkers of canonical relevance. Generally concluding that LDH, indirect bilirubin, haptoglobin and reticulocytosis are present in characteristic, biologically consistent trends across HA subtypes, is consistent with mechanistic expectation and guidance already reported [11]. Our data validate the role of LDH and haptoglobin in intravascular hemolysis (PNH) and reticulocytosis and unconjugated hyperbilirubinemia in extravascular hemolysis (AIHA and HS). In AIHA, the DAT variants correlate with the extent of hemolysis and support the view in the literature that DAT is a "cornerstone" (even though the results are not independent from the methodology [12]). Enhanced and alternative DAT techniques could detect otherwise DAT-negative cases, and eluate testing is used to improve the specificity of interpretation, in those patients who give positive test with polyspecific reagents for which the clinical setting is uncertain.

"Our findings augment these findings by associating higher DAT grading on lower haptoglobin and higher bilirubin, independent of Hb, which supports the idea of the above-discussed

translation of immunologic reactivity to a quantifiable biochemical surrogate biomarker of hemolysis." The PNH subgroup had the highest levels of LDH and plasma free hemoglobin which is consistent with complement-mediated intravascular lysis and the established diagnostic algorithms with high sensitivity flow cytometry for CD55/CD59 deficiency [13]. The direct relationship with clinic-risk and biochemical hemolysis (explained by clonal burden) of chromosomes-size is consistent with other reports. Although this study was not conducted as a therapy test, newer complement inhibitors, especially the terminal complement or proximal complement automediator inhibitors, reduce hemolysis and LDH and this signature of the biomarkers correlates with the therapy monitoring systems. The presence of high MCHC and reticulocytosis was consistent with high description in guidelines in relation to membrane loss and values sequestration in sickle hemoglobinopathy (HS). Schistocytic focus was not part of HS ICSH, but gives context to the diagnostic setting for the fragmented cell finding of TMA (more fragmented cells, normal bilirubin, and high LDH) and those G6PD deficient who have alternating periods of normal or normal elbow k (alternating periods of elbow K+ okayed LDH, transient haptoglobin suppression). This dynamic behavior favors the position that repeated investigation for enzymes could be sensitive enough to be false negative in acute hemolysis, and investigation in the acute setting could be the only acceptable sampling in acute hemolysis.

Importantly, the composite hemolysis score was used superiorly to single parameters for (a) the discrimination between HA and health and (b) the prediction of severe anemia and hyperhemolysis. Other authors have discussed the limitations of any particular biomarker - LDH is not specific for RBC lysis; haptoglobin is an acute phase reactant; bilirubin can be increased by nonhemolytic causes [15]. In sickle cell disease, composite indices that include "hemolysis index" are associated with adverse outcomes and death. The triad is simple and provides pragmatically useful advantages, which does not need a great platform and can be applied in most laboratories. It has arguably great clinical utility in resource limited settings where confirmatory tests are staged.

Clinical implications are including (i) etiological clues (eg. very high LDH activity, not detectable haptoglobin immunochemistry) to PNH work-out (even if the anemia is very slight), (ii) routine to offer first line panel for suspected hemolysis with CBC with R, LDH, indirect bilubin, haptoglobin so further and (iii) a judicious use of DAT and flow cytometry based on a composite risk. Besides their operational utility, the patterns have strengths that are felt important for teaching their pathophysiology, which correlates with intravascular vs. extravascular clearance, complement activation, and marrow response. Limitations from single center design and relatively small number of samples from each etiology, including PNH and HS are limitations. Exclusion of recent transfusion is an absolute precondition to avoid confounding; however, the patient population might be limited to acutely managed inpatients. We did not measure schistocytes or reticulocyte haemoglobin content which would further characterize microangiopathy or erythropoiesis iron restriction [16-17]. Finally, the composite score needs to be validated and calibrated between laboratories. Conclusions: These results suggest that no composite index should be used, reticulocyte hemoglobin content and carboxyhemoglobin have to be included in the panels, and biomarker tracts should be prospectively evaluated as surrogate endpoints in clinical trials of complement- and B cell-directed therapies in meta-analyses.

Conclusion

In a prospective ethics-permitted cohort, complete hemolysis markers showed a different quantitative expression of the different causes of the disease mechanism: LDH, haptoglobin, was the most important marker to differentiate intravascular hemolysis (mainly PNH) while reticulocytosis and unconjugated bilirubin were the most prevalent in AIHA, HS. A combined composite score using LDH, indirect bilirubin, and inverse haptoglobin was a better discriminator and a better predictor of severity compared with any of the parameters alone. These data underline the value of panel-based evaluation performed on ongoing tools and made aware of etiology and can be a realistic, generalizable framework for triage and monitoring in hemolytic anemia.

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