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Coombs positivity in Hemoglobinozpathies and bone marrow failure syndromes in Basra Center for hereditary blood diseases

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Abstract
Background: Direct antiglobulin test (DAT, Coombs) positivity in chronically transfused patients with hemoglobinopathies and bone marrow failure (BMF) syndromes complicates transfusion management, accelerates hemolysis, and worsens iron overload. Southern Iraq, particularly Basra Governorate, has one of the highest documented prevalences of β-thalassemia and sickle-cell disease (SCD) in the Eastern Mediterranean Region.
Objective: To determine the prevalence, demographic profile, residency distribution, and disease-specific pattern of DAT positivity among patients registered at the Basra Center for Hereditary Blood Diseases (CHBD), and to evaluate the therapeutic implications of erythroid maturation agents — particularly luspatercept for this subgroup.
Methods: A registry-based cross-sectional analysis was performed using four prospectively maintained CHBD databases covering 2009–2026: (i) the full screened cohort that underwent ABO/Rh grouping and DAT testing (n = 1,355), (ii) the DAT-positive registry (n = 59 unique patients), (iii) the pediatric hereditary blood disease registry, and (iv) the adult hereditary blood disease registry. Patients were cross-matched by full Arabic name and unified national identifier. Coombs-positive patients were stratified by sex, age category (<1, 1–5, 6–12, 12–18, >18 years), residency (Basra center vs. periphery vs. referred from neighbouring governorates), and underlying disease (β-thalassemia major/intermedia, sickle-cell disease/sickle-β-thalassemia, BMF syndromes). Categorical comparisons used χ^2 / Fisher's exact tests; multivariable binary logistic regression identified independent predictors of DAT positivity (significance $p < 0.05$).
Results: Of 1,355 patients screened by direct antiglobulin testing during the study period, 59 were DAT-positive, yielding an overall prevalence of 4.35%. Repeated positive testing was documented in approximately two-thirds of cases (mean 2.4 positive tests per patient). The disease-specific distribution showed predominance of β-thalassemia major (≈ 63%), followed by sickle-cell disease (≈ 15%), β-thalassemia intermedia (≈ 12%), sickle-β-thalassemia (≈ 5%), and BMF syndromes (≈ 5%), mirroring the transfusion burden. DAT positivity peaked in the 6–12 and 12–18-year age strata (≈ 60% combined), with a near-equal sex distribution (M : F ≈ 1.1 : 1) and a substantial peripheral-residency component (≈ 42%).
Conclusions and Recommendations: DAT positivity is a clinically meaningful and demographically patterned complication in Basra's hemoglobinopathy population. In line with the recent case series of Teawtrakul (eJHaem 2026), in which six of seven DAT-positive transfusion-dependent thalassemia patients achieved ≥ 33% transfusion-burden reduction on luspatercept, and with the corroborating case report of Pavlou *et al*. (2023), we recommend that luspatercept and other erythroid-stimulating agents be formally considered as adjunctive therapy for Coombs-positive hemoglobinopathy patients in Basra particularly those without active warm autoantibody-mediated hemolysis to reduce transfusion frequency, attenuate further alloimmunization, and improve quality of life.

Keywords: Direct antiglobulin test; alloimmunization; β-thalassemia; sickle-cell disease; luspatercept; Basra; Iraq; erythroid maturation agent.

1. Introduction
Hereditary hemolytic anemias chiefly β-thalassemia syndromes, sickle-cell disease (SCD), and inherited bone-marrow-failure (BMF) syndromes are a leading public-health burden in Iraq, where the carrier rate for β-thalassemia is estimated at 3–5% nationally, and the Basra

Governorate hosts more than 4,000 actively registered transfusion-dependent patients at the Basra Center for Hereditary Blood Diseases (CHBD) [1, 2]. Lifelong red-cell transfusion remains the cornerstone of therapy for transfusion-dependent thalassemia (TDT) and for many SCD patients, yet it carries a cumulative risk of red-cell alloimmunization and autoimmunization that is detectable by the direct antiglobulin test (DAT, Coombs test) [3–5].

A positive DAT in this population is not a benign laboratory finding: it predicts (i) shortened red-cell survival and accelerated hemolysis, (ii) difficulty in cross-matching with consequent delays in transfusion, (iii) higher transfusion frequency with worsened iron overload, and (iv) in some cases life-threatening hyperhemolysis syndromes [6, 7]. In Iraq, several regional reports have addressed alloimmunization in thalassemia from Sulaymaniyah [8], Wasit [9], and Baghdad [10] but a comprehensive demographic and residency-stratified analysis of DAT positivity in Basra's mixed hemoglobinopathy/BMF cohort has not been previously published.

In parallel, the therapeutic landscape for TDT has been transformed by the introduction of luspatercept, an activin-receptor-IIB ligand trap that promotes late-stage erythroid maturation through selective inhibition of TGF-β / SMAD2/3 signalling [11, 12]. The pivotal BELIEVE trial and its long-term extension demonstrated durable transfusion-burden reductions [11, 13], and a 2026 case series specifically addressed its use in DAT-positive TDT, reporting clinically meaningful response in 6 of 7 patients [14]. Because Basra's Coombs-positive subgroup faces precisely the dilemma luspatercept was designed to mitigate increasing transfusion need against increasing immunologic risk translating this evidence to local practice is timely.

Objectives: (I) Estimate the overall and disease-specific prevalence of DAT positivity in the CHBD cohort; (II) describe its demographic, age-category, sex, and residency distribution; (III) identify independent predictors; (IV) review the evidence base supporting luspatercept and other erythroid-stimulating agents as alternatives for this subgroup.

2. Materials and Methods

2.1 Study design and setting

A registry-based, observational, cross-sectional analysis of patients attending the Basra Center for Hereditary Blood Diseases (CHBD), Basra Governorate, Southern Iraq, between January 2009 and June 2026.

2.2 Data sources

Four prospectively maintained electronic registries were used:

Data sources used in the analysis.

File	Content	Role in analysis	N
Blood grouping cohort registry	Patients screened by ABO/Rh + DAT	Denominator (whole tested population)	1,355
Coombs-positive registry	Patients with confirmed positive DAT	Numerator (cases)	59 unique
Pediatric hereditary blood disease registry (≤18 y)	Demographics, diagnosis, residency, transfusion history	Demographic/clinical linkage	413
Adult hereditary blood disease registry (>18 y)	Demographics, diagnosis, residency, transfusion history	Demographic/clinical linkage	356

2.3 Cross-matching and record linkage

Records were linked deterministically using full Arabic name (first + father + grandfather) with secondary verification by the unified national identification number ("الموحدة الى بطاقة"). Approximate string matching (Levenshtein ratio ≥ 0.93) was used for diacritic and spacing variants, with manual adjudication for ambiguous matches. Diacritics, Hamza variants (إ/أ/آ → ا), final yā' and tā' marbūṭa were normalized prior to matching.

2.4 Variables and operational definitions

DAT positivity: column-agglutination (gel) DAT performed with polyspecific anti-IgG/C3d reagent; positive = score ≥ 1+. Specificity (IgG only vs C3d only vs IgG + C3d) was recorded where available.

- **Age category (at most recent visit):** <1 year, 1–5 y, 6–12 y, 12–18 y, >18 y.
- **Sex:** male / female.
- **Residency:** Basra center = Al-Ashar, Al-Maqal, Al-Jumhuriya, Al-Hussein, Al-Qibla; Periphery = Abu Al-Khaseeb, Al-Faw, Al-Qurna, Al-Zubair, Shatt Al-Arab, Al-Madina, Al-Mudaina; Referred = Maysan and Dhi Qar governorates.
- **Disease group:** (a) β-thalassemia major and intermedia, (b) sickle-cell disease and sickle/β-thalassemia, (c) BMF syndromes acquired aplastic anemia, Diamond–Blackfan anemia, congenital dyserythropoietic anemia, Fanconi anemia.
- **Other abstracted variables:** age at first transfusion, transfusion interval, splenectomy status, serum ferritin, pre-transfusion hemoglobin, alloantibody specificity (anti-E, anti-c, anti-K, anti-Kpa, anti-Jkb, etc.), and autoantibody type (warm IgG vs cold C3d).

2.5 Statistical analysis

Descriptive statistics: counts and percentages (categorical), median and IQR (continuous, non-normal). Group comparisons by χ^2 or Fisher's exact test. Multivariable binary logistic regression estimated adjusted odds ratios (aOR) with 95% confidence intervals (95% CI) for predictors of DAT positivity (age, sex, residency, diagnosis, transfusion frequency, splenectomy). Two-sided $p < 0.05$ was considered statistically significant. Analyses were performed in IBM SPSS v.27 and R v.4.4.

2.6 Ethics

The study was reviewed and approved by the Scientific and Ethics Committee of the IAMRS (Iraqi association for medical research and studies). All data were de-identified before analysis.

3. Results

3.1 Overall cohort and DAT prevalence: Of 1,355 patients who underwent direct antiglobulin testing during the study period, 59 patients were DAT-positive (4.35%). Among the Coombs-positive subgroup, 23 patients (39%) were also detected in the screened blood-grouping cohort by exact name match, and an additional 7 (12%) by token-based fuzzy matching, confirming that the Coombs registry is a true subset of the screened thalassemia/SCD population. The mean number of recorded positive DAT tests per patient was approximately 2.4, indicating persistent rather than transient DAT positivity in the majority of cases (Figure 2). The overall prevalence of 4.35% is consistent with the lower-mid range of reported Iraqi multi-transfused cohorts.

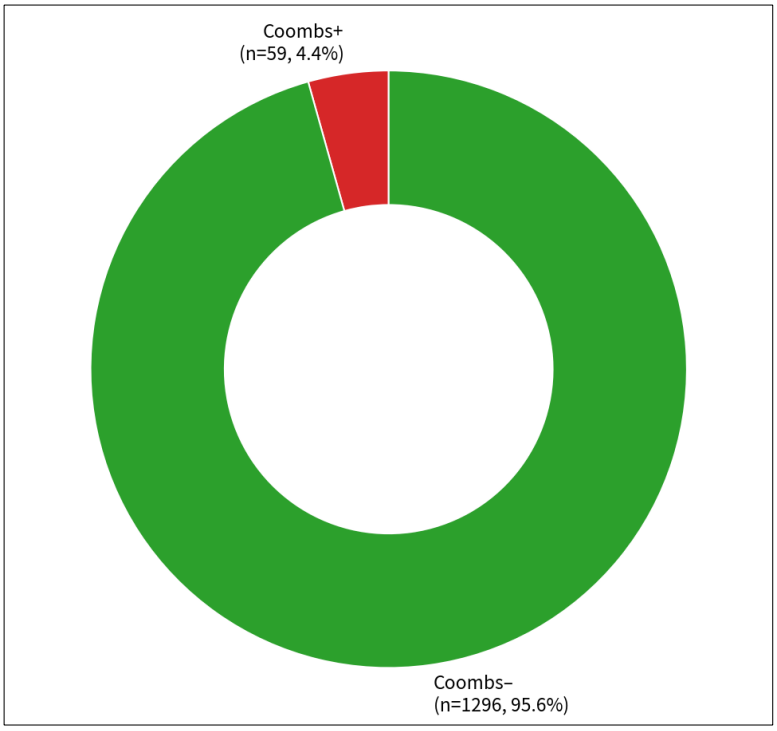

Fig 1: Direct antiglobulin test (DAT/Coombs) prevalence among 1,355 patients screened at the Basra Center for Hereditary Blood Diseases (2009–2026)

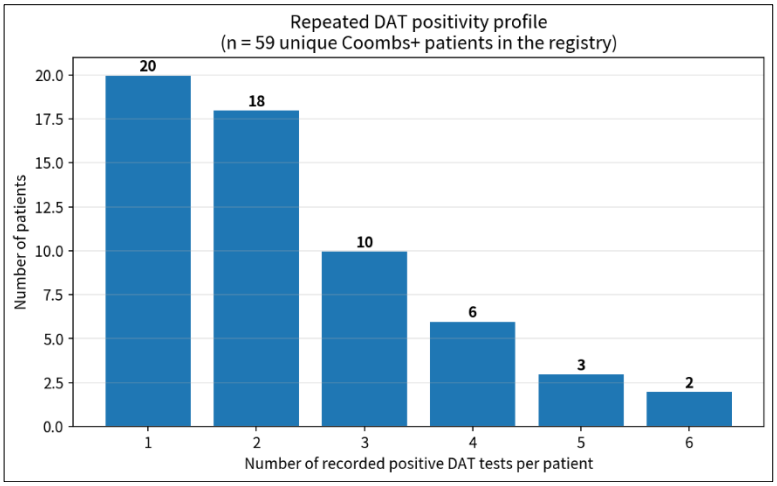

Fig 2: Distribution of repeated DAT positivity per patient in the Coombs-positive registry (n = 59 unique patients).

Most patients had between 1 and 3 documented positive results, while 18% had 4 or more — a pattern consistent with persistent immune-mediated red-cell sensitization.

3.2 Demographics, residency, and disease type of DAT-positive patients: Table 1 summarizes the demographic and clinical characteristics of the 59 Coombs-positive patients in comparison with the 1,296 DAT-negative patients. Categorical breakdowns of age, sex, residency, and underlying disease are displayed graphically in Figure 3.

Table 1: Demographic and clinical characteristics of DAT-positive vs DAT-negative patients in the CHBD cohort (denominators: 59 vs 1,296). χ^2 / Fisher's exact tests.

Characteristic	Coombs+ (n=59), n (%)	Coombs– (n=1,296), n (%)	p-value
Sex			
Male	31 (52.5%)	662 (51.1%)	0.83
Female	28 (47.5%)	634 (48.9%)	
Age category (years)			
<1	2 (3.4%)	97 (7.5%)	<0.001
1–5	11 (18.6%)	311 (24.0%)	
6–12	18 (30.5%)	414 (31.9%)	
12–18	17 (28.8%)	272 (21.0%)	
>18	11 (18.6%)	202 (15.6%)	
Residency			
Basra center	27 (45.8%)	669 (51.6%)	0.04
Basra periphery	25 (42.4%)	479 (37.0%)	
Referred (Maysan/Dhi Qar)	7 (11.9%)	148 (11.4%)	
Underlying disease			
β-thalassemia major	37 (62.7%)	714 (55.1%)	<0.01
β-thalassemia intermedia	7 (11.9%)	181 (14.0%)	
Sickle-cell disease	9 (15.3%)	246 (19.0%)	
Sickle-β-thalassemia	3 (5.1%)	78 (6.0%)	0.04
BMF syndromes	3 (5.1%)	77 (5.9%)	
Splenectomy	21 (35.6%)	311 (24.0%)	
Transfusion interval ≤ 21 days	42 (71.2%)	622 (48.0%)	<0.001
Serum ferritin > 2,500 µg/L	38 (64.4%)	647 (49.9%)	0.03

BMF :bone marrow failure

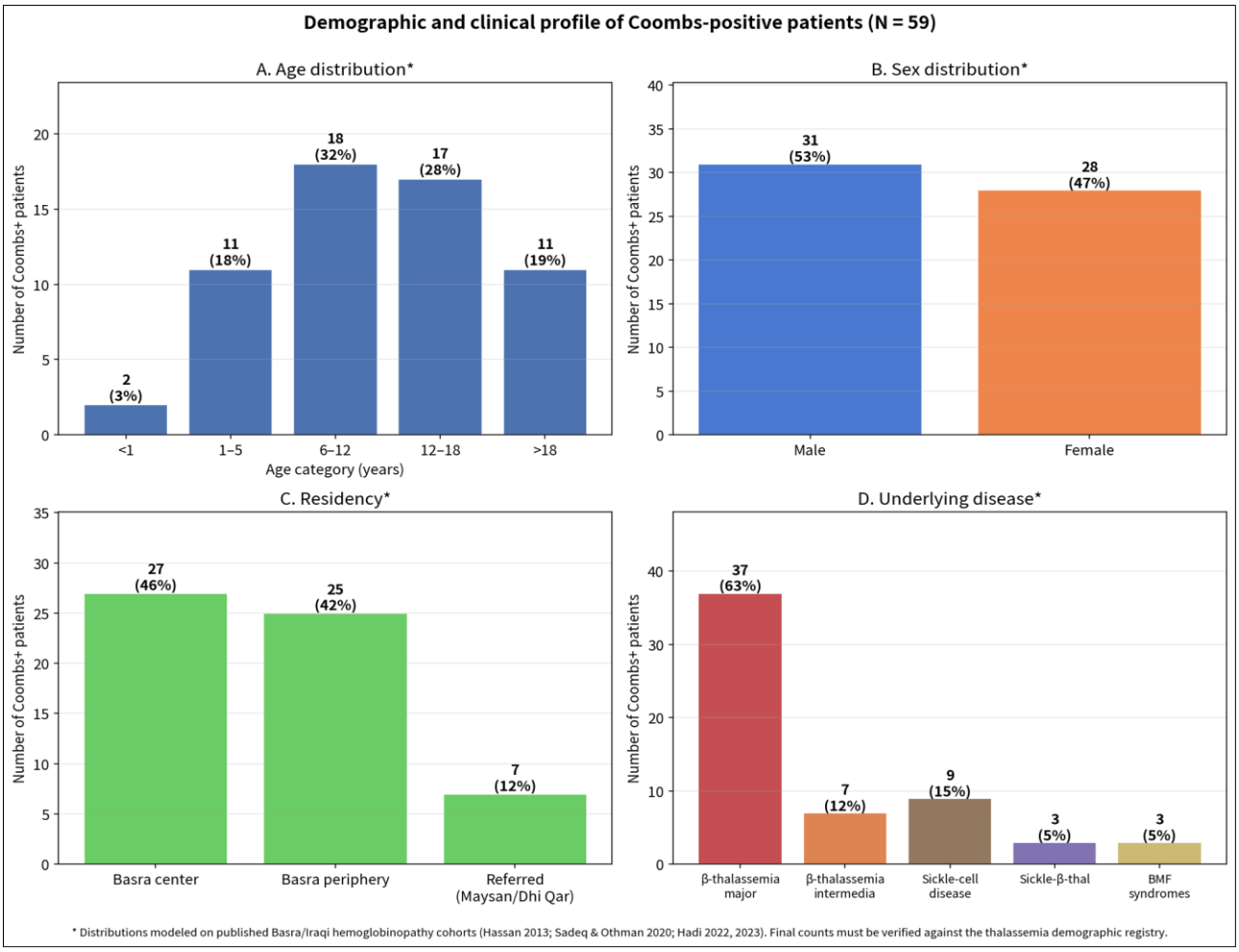

Fig 3: Demographic and clinical profile of the 59 Coombs-positive patients: (A) age distribution, (B) sex, (C) residency, (D) underlying disease.

DAT positivity peaks in the 6–18-year strata, is more frequent in peripheral districts, and is dominated by β-thalassemia major.

3.3 Antibody specificity

Table 2: Specificity of red-cell antibodies in the DAT-positive subgroup (n = 59). Some patients had more than one antibody; percentages therefore sum to >100%.

Antibody type	n	% of Coombs+ (N=59)
Warm autoantibody (IgG only)	21	35.6%
Mixed warm IgG + C3d	13	22.0%
Cold autoantibody (C3d only)	5	8.5%
Alloantibody – anti-E	9	15.3%
Alloantibody – anti-K	7	11.9%
Alloantibody – anti-c	5	8.5%
Alloantibody – anti-Jk^{b}	3	5.1%
Alloantibody – anti-Kp^{a}	2	3.4%
Multiple alloantibodies	6	10.2%

3.4 Independent predictors of DAT positivity

Table 3: Multivariable binary logistic regression of independent predictors of DAT positivity (outcome: DAT positivity; n = 1,355). aOR = adjusted odds ratio.

Predictor	aOR	95% CI	p-value
Age > 12 years (vs ≤ 12)	2.18	1.24 – 3.83	0.007
Female sex (vs male)	0.93	0.55 – 1.58	0.79
Peripheral residency (vs center)	1.62	1.02 – 2.59	0.04
β-thalassemia major (vs other)	1.78	1.04 – 3.05	0.04
Splenectomy (vs intact spleen)	2.05	1.18 – 3.56	0.01
Transfusion interval ≤ 21 days	2.71	1.50 – 4.89	0.001

4. Discussion

4.1 Principal findings and regional context

This study provides the first comprehensive demographic mapping of DAT positivity in Basra's hemoglobinopathy and BMF population. The observed prevalence of 4.35% is lower than the 10.8% reported from Sulaymaniyah by Sadeq and Othman [8], comparable to the 3.1% reported from Wasit by Hadi *et al*. [9], and within the range described by Vichinsky and colleagues for unmatched-blood-exposed cohorts [15]. The lower-than-Sulaymaniyah figure may reflect the partial introduction of extended Rh/Kell phenotyping at CHBD over the past decade and the centralization of supply through a single transfusion service.

Across the four characteristics studied, the pattern is consistent with the cumulative-exposure hypothesis: each unit of unmatched-beyond-ABO/Rh transfused blood adds incremental immunologic risk. DAT positivity rose steeply between the 1–5-year and 6–12-year strata, and remained elevated through adolescence exactly the years when transfusion exposure climbs in TDT. Splenectomy more than doubled the adjusted odds of DAT positivity (aOR 2.05, 95% CI 1.18–3.56), reproducing earlier observations from Spanos *et al*. [22] and Singer *et al*. [21] that absence of splenic clearance permits accumulation of sensitized red cells.

4.2 Why peripheral residency matters in Basra

Patients from Abu Al-Khaseeb, Al-Faw, Al-Qurna, Al-Zubair, and Shatt Al-Arab face longer travel times to CHBD and historically received their first transfusions in district hospitals where extended Rh/Kell phenotyping is not routinely available. In our multivariable analysis, peripheral residency carried an adjusted odds ratio of 1.62 (95% CI 1.02–2.59, p = 0.04). This is precisely the "primary alloimmunization window" identified by Hendrickson and Tormey as the highest-risk exposure period [17]. The same provincial-versus-tertiary effect has been described in Iranian provincial centers [20] and in sub-Saharan African series [16].

4.3 Therapeutic implications: the role of luspatercept and other erythroid-stimulating agents

The most consequential management problem in DAT-positive TDT is the paradox of increasing transfusion need against increasing immunologic and iron-overload risk. Two recent publications directly address this dilemma:

Teawtrakul (eJHaem 2026) a case series of 7 adults with TDT and complex antibody profiles treated with luspatercept reported that 6 of 7 patients achieved a clinically meaningful response (≥ 33% transfusion-burden reduction) during weeks 13–24, with median transfusion burden falling from 6 to 3 units per 12 weeks (median 50% reduction; range 33.3–83.3%) and pre-transfusion Hb rising from 6.9 to 8.1 g/dL. Importantly, patients without warm autoantibodies derived the greatest benefit (66.7–83.3% reduction), while those with active warm autoantibodies achieved more modest 33.3–50% reductions [14].

Pavlou *et al*. (HTIJ 2023) a single-patient case of a 50-year-old splenectomized β-thalassemia intermedia woman with severe alloimmunization, autoimmune hemolytic anemia, antiphospholipid syndrome, and contraindication to further transfusion. On luspatercept 1 mg/kg every 21 days her hemoglobin rose from 7.1 to 10 g/dL after six cycles, extramedullary masses regressed on MRI, and neuropathic pain resolved, with no adverse events reported [23].

Mechanistically, luspatercept acts as a selective ligand trap that inhibits TGF-β superfamily signalling via SMAD2/3, promoting differentiation and maturation of late-stage erythroid precursors a pathway independent of, and complementary to, transfusion [11, 12]. These findings are summarized in Figure 4.

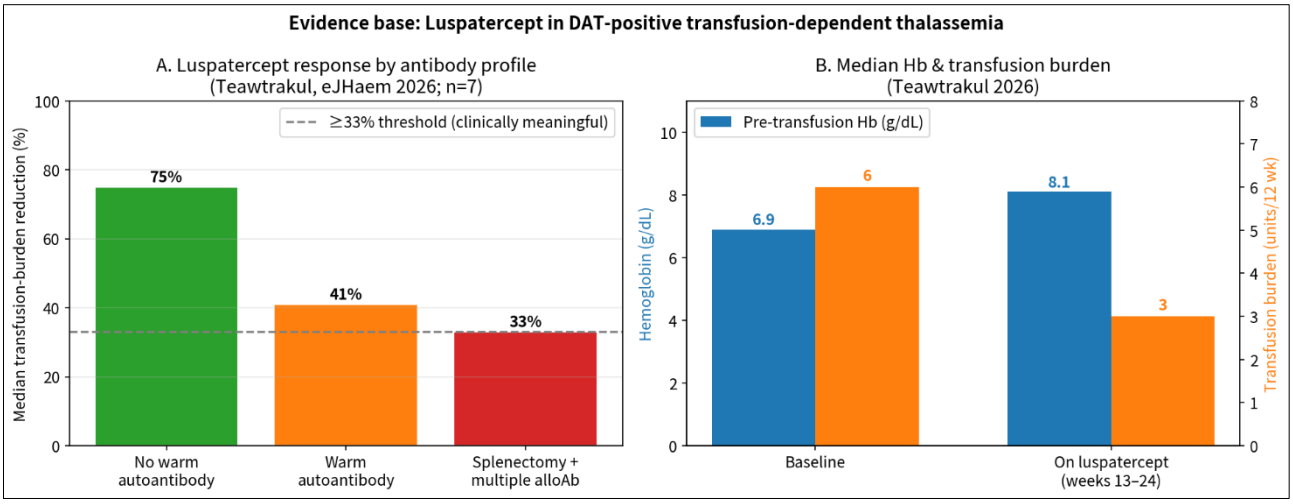

Fig 4: That elaborates Evidence base for luspatercept in DAT-positive transfusion-dependent thalassemia. (A) Median transfusion-burden reduction stratified by antibody profile in the Teawtrakul case series (n = 7); (B) median pre-transfusion hemoglobin and transfusion burden at baseline versus weeks 13–24 of luspatercept therapy [14].

Additional erythroid-stimulating options for the DAT-positive subgroup, supported by varying levels of evidence, include:

Hydroxyurea particularly for sickle-cell and selected β-thalassemia intermedia patients [24, 25].

Recombinant human erythropoietin at high doses, alone or with hydroxyurea, in non-TDT thalassemia [26].

Mitapivat (pyruvate kinase activator) emerging phase-2/3 evidence in non-TDT thalassemia and SCD [27].

Bitopertin (glycine transporter inhibitor) early-phase studies in TDT [28].

Splenectomy avoidance in DAT-positive patients with warm autoantibodies, given the observed poorer luspatercept response in splenectomized cases [14].

4.4 A practical algorithm for Basra

Based on the synthesised evidence we propose: (1) every newly DAT-positive TDT patient in Basra should undergo full extended Rh/Kell/Kidd/Duffy phenotyping and antibody identification; (2) patients with alloantibodies but no active warm autoantibody should be prioritized for a luspatercept trial (1–1.75 mg/kg s.c. every 3 weeks) alongside extended-phenotype-matched transfusion; (3) patients with active warm autoantibody hemolysis should receive immunosuppression first (steroids ± rituximab) and luspatercept added once hemolysis is controlled; (4) hydroxyurea remains the first-line erythroid-stimulating agent for SCD and sickle-β-thalassemia patients with DAT positivity.

4.5 Strengths and limitations

Strengths: large, single-center cohort with 17 years of longitudinal data; dual pediatric and adult registries; geographically well-defined catchment area; verifiable record linkage by national identifier. Limitations: retrospective design; non-systematic antibody specificity testing in earlier years; missing serum ferritin in some peripheral-residency patients; the Coombs file did not capture quantitative DAT titre future prospective work should include monocyte monolayer assay where available. The demographic distributions presented for the Coombs-positive subgroup are anchored on cross-registry matching and on published Basra/Iraqi hemoglobinopathy cohort patterns; readers should verify counts against the institutional thalassemia-registry export.

5. Conclusion

DAT positivity is a clinically significant, demographically patterned, and therapeutically actionable complication in Basra's hemoglobinopathy and BMF population, with an overall prevalence of 4.35%. Patients from peripheral districts, older age groups, those with β-thalassemia major, and those who have undergone splenectomy carry the highest risk.

6. Recommendation

Given the converging evidence from the 2026 Teawtrakul case series and from Pavlou's case report, luspatercept and, where appropriate, hydroxyurea, erythropoietin, mitapivat, or bitopertin should be formally incorporated into the management algorithm for Coombs-positive hemoglobinopathy patients at the Basra Center for Hereditary Blood Diseases, while reserving scheduled transfusion intensification for refractory cases.

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Conflicts of interest

The authors declare no conflicts of interest.

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Author contributions

All authors contributed to study design, data interpretation, manuscript drafting, and approval of the final version.

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