Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Patient-reported outcome measures in adult patients with autoimmune hemolytic anemia and immune thrombocytopenia: a systematic review with meta-analysis

Giacinto Luca Pedone
Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico
Esther Natalie Oliva
London North West University Healthcare NHS Trust
Bruno Fattizzo
bruno.fattizzo@unimi.it

Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico

Research Article

Keywords: Fatigue, Meta-analysis, Autoimmune hemolytic anemia, Immune thrombocytopenia, Quality of life

Posted Date: November 23rd, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11486033/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License

Additional Declarations: Competing interest reported. G.L.P. received lecture fess or congress support from Alexion Pharmaceuticals, Avanzanite Biosciences BV, Novartis, Recordati Rare Diseases, and Roche. E.N.O. reports receiving consultancy/speaker bureau fees from Alexion Pharmaceuticals, Bristol Myers Squibb, Daiichi Sankyo, Janssen, Novartis, Pfizer, Ryvu Therapeutics, Sanofi, Sobi, and Syros Pharmaceuticals; and patents and royalties from Bristol Myers Squibb, Halia Therapeutics, and Ryvu Therapeutics. B.F. received consultancy and speaker's bureau from Alexion, AstraZeneca, Janssen, Novartis, Recordati, Roche, and Sanofi.

Abstract

Background

Patient-reported outcome measures (PROMs) are increasingly incorporated into trials of novel therapies for autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP).

Objectives

To determine whether biomarker response translates into benefit in patient-reported fatigue and quality of life, comparing the concordance between single-arm and placebo-controlled studies.

Methods

We conducted a systematic review and random-effects meta-analysis of the relationship between biomarker response and PROMs, searching PubMed, EMBASE, and CENTRAL up to March 2026.

Results

Ten AIHA and 24 ITP studies were included. In AIHA, the pooled FACIT-Fatigue change from baseline across eight single-arm treatment cohorts was + 9.2 points (95% CI 7.9–10.5; I^2=0%), exceeding the clinically important change threshold, whereas the pooled between-group difference from three placebo-controlled randomized trials was + 4.2 points (95% CI − 7.6–16.1; I^2=67%), with a confidence interval crossing zero and a pooled placebo-arm change of + 2.1 points. Fatigue improvement was greater in cold agglutinin disease than in warm AIHA (9.9 vs 7.3 points), and hemoglobin change was associated with FACIT-Fatigue change (+ 3.2 points per g/dL; 95% CI 0.5–5.9; pooled r = 0.64). In ITP, the pooled between-group FACIT-Fatigue difference was null (+ 0.6 points; 95% CI − 3.2–4.4; I^2=74%), while the disease-specific ITP-PAQ Fatigue domain showed a larger but non-significant difference (+ 8.6 points; 95% CI − 5.2–22.4).

Conclusions

Biomarker–PROM concordance was inconsistent within both diseases. Correcting hemoglobin or platelet counts appears necessary but not sufficient for fatigue improvement. The hemoglobin–fatigue association in AIHA and the platelet–fatigue dissociation in ITP support integrating disease-specific PROMs into future trials.

Introduction

The systematic evaluation of patient-reported outcome measures (PROMs) has long been integral to oncological drug development, where health-related quality of life (HRQoL) endpoints inform both regulatory approval and clinical practice[1]. In contrast, the clinical trials for non-malignant hematologic disorders, including autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP), have historically relied almost exclusively on laboratory surrogates to define therapeutic success. Whether normalizing hemoglobin (Hb) or achieving a safe

platelet (PLT) count translates into meaningful symptomatic relief remains an open question that is increasingly relevant as novel targeted agents reshape the therapeutic landscape of autoimmune cytopenias[2].

AIHA encompasses cold agglutinin disease (CAD), warm AIHA (wAIHA), and mixed forms, each characterized by autoantibody-mediated red blood cell destruction[3]. Beyond anemia, known to be associated with asthenia and shortness of breath, other pathophysiological mechanisms may contribute to the perceived fatigue in wAIHA. In CAD, chronic complement activation sustains an inflammatory milieu that produces debilitating fatigue as the dominant patient-reported symptom burden, often disproportionate to anemia severity. In wAIHA, extravascular hemolysis and the iatrogenic effects of long-term corticosteroid exposure impair physical functioning through mechanisms that may only partially resolve with Hb normalization. ITP, defined by immune-mediated platelet destruction and impaired megakaryopoiesis[4,5], presents a qualitatively different symptom profile: the primary clinical risk is bleeding, yet patients consistently report fatigue, anxiety related to unpredictable bleeding, and activity restriction as the most burdensome aspects of their disease. The I-WISh survey, encompassing 1507 patients across 13 countries, found that 42% reported impaired energy levels “more than half the time” or “all the time,” and that increasing energy was ranked among the top three treatment goals[6]. Critically, the relationship between PLT count and these patient-reported symptoms is not straightforward: bleeding risk and symptom burden are known to be discordant with PLT counts, and the pathophysiology of ITP-related fatigue, whether mediated by subclinical bleeding, inflammatory cytokines, or treatment side effects, remains incompletely understood.

PROMs provide standardized, validated instruments for capturing the patient’s subjective health status without clinician interpretation[7]. In autoimmune cytopenias, the most used instruments such as the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-Fatigue) scale, the ITP Patient Assessment Questionnaire (ITP-PAQ), the 36-Item Short Form Survey (SF-36), and the Functional Assessment of Cancer Therapy-Thrombocytopenia 6-item (FACT-Th6), were largely developed or repurposed from oncological settings. The FACIT-Fatigue, for example, was validated specifically for CAD patients only in 2025[8], and no disease-specific PROM exists for wAIHA. In ITP, the ITP-PAQ captures domain-specific symptom burden including fatigue, anxiety, and activity limitation; however, its development predates the current therapeutic era and may not fully reflect the experiences of patients treated with novel agents. This heterogeneity in PROM selection across trials introduces substantial analytical challenges when attempting cross-study comparisons.

The present study is a systematic review and meta-analysis of the relationship between biomarker response and PROM outcomes in AIHA and ITP.

Methods

A systematic review reported according to PRISMA 2020[9] was conducted, searching PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception to March 2026 (full search strategy in Supplementary Methods). Studies were included if they enrolled adults with wAIHA, CAD, or ITP, reported at least one validated PROM, and were peer-reviewed original research (RCTs, observational cohorts, or cross-sectional studies); case reports, editorials, studies without PROM data, and non-English publications were excluded. Titles and abstracts, then full texts, were screened independently by two reviewers, with disagreements resolved by consensus.

Extracted variables included study design, disease subtype, sample size, PROM instruments, arm-level means and standard deviations for PROM change from baseline, biomarker response metrics (Hb change for AIHA; PLT response rate for ITP), and reported correlation coefficients. Where dispersion measures were missing, standard errors were reconstructed from 95% CIs, p-values, or medians/IQR using the Wan estimators and fatigue scores were harmonized across instruments using established crosswalks in sensitivity pools; all derivation and harmonization rules are detailed in Supplementary Methods. Methodological quality was assessed with the Cochrane Risk of Bias 2.0 tool, ROBINS-I, and the Newcastle–Ottawa Scale, and certainty of evidence for each pooled outcome with GRADE (references for all methodological tools are provided in Supplementary Methods).

Analyses were conducted in R v.4.5.2 using the meta and metafor packages, with random-effects models and restricted maximum-likelihood estimation of between-study variance throughout; for pools of fewer than 10 studies the Hartung–Knapp small-sample variance adjustment was applied (Supplementary Methods). For AIHA, the primary analysis pooled the mean FACIT-Fatigue change from baseline (CFB) across single-arm treatment cohorts (inverse-variance mean difference [MD]); between-group MDs from placebo-controlled RCTs and a separately pooled placebo/control component were secondary analyses. For ITP, between-group MDs were pooled separately for FACIT-Fatigue and the ITP-PAQ Fatigue domain, with a prespecified sensitivity analysis excluding the crosswalked VAYHIT2 data. Fatigue improvements were interpreted against clinically important change (CIC) benchmarks (FACIT-Fatigue ≥ 3 points[10]; ITP-PAQ Fatigue ≥ 8 points).

Biomarker–PROM concordance was assessed primarily by a continuous standardized within-trial comparison of biomarker versus PROM effects (summarized as a “concordance gap”) and by random-effects meta-regression of arm-level FACIT-Fatigue change on Hb change. A descriptive four-category concordance classification of each treatment arm (Tables 1 and 2), pooled Hb–FACIT-Fatigue correlations, leave-one-out influence and CAD-versus-wAIHA subgroup analyses, and qualitative assessment of washout/re-challenge data as a test of reversibility, are detailed in Supplementary Methods.

Table 1
PROM and biomarker results in AIHA studies

Drug (study)	Design	N	PROM	PROM result	Hb result	Concordance
Sutimlimab (CARDINAL Part A)[11]	OL SA, CAD	24	FACIT-F	Mean Δ + 10.9 (95% CI 8.0–13.7) at TAT; 90% achieved CIC	LS mean ΔHb + 2.6 g/dL (0.7–4.5)	Concordant (+)
Sutimlimab (CARDINAL Part B, 2y)[12]	OLE, CAD	22	FACIT-F, SF-12, EQ-5D	W135 Δ + 11.7 (SE 3.7); reversible on washout	Last-available Hb ~ + 3.6 g/dL	Concordant (+)
Sutimlimab (CADENZA Part A)[13,14]	RCT DB, CAD	42	FACIT-F	Between-group MD + 8.9 (4.0–13.9; p < 0.001)	LS ΔHb + 2.66 vs + 0.09 (MD 2.56)	Concordant (+)
Sutimlimab (CADENZA Part B)[15]	OLE, CAD	39	FACIT-F	Switchers + 8.0; last visit + 8.8; washout − 1.4	PBO→suti Hb reached 11.7 g/dL	Concordant (+)
Pegcetacoplan (phase 3, CASCADE, NCT05096403)[17]	RCT DB → OLE, CAD	24	FACIT-F, FACT-An, SF-12	Between-group MD + 0.93 (< CIC); PBO arm + 8.8	ΔHb MD + 1.49 g/dL (> CIC)	Discordant-PROM
Pegcetacoplan (PLAUDIT, phase 2)[16]	OL SA, wAIHA + CAD	24	FACIT-F, LASA	CAD W8 + 10.5; wAIHA W8 + 8.0	ΔHb + 2.4 (CAD), + 2.7 (wAIHA)	Concordant (+)
Iptacopan (phase 2 basket)[18]	OL SA, CAD	10	FACIT-F	Mean Δ + 8.8 (range 2–16)	Hb increase + 2.2 g/dL	Concordant (+)
Rilzabrutinib (LUMINA-2, phase 2b)[19,20]	OL SA, wAIHA	22	FACIT-F	W24 + 7.0; IL-10 negatively correlated	Hb increase ≥ 2 in 64%	Concordant (+)
Sovleplenib (ESLIM-02, phase 2)[22]	RCT DB, wAIHA	21	FACIT-F total, SF-36	W8 total + 8.7 vs − 15.0 (PBO)	Hb increase + 2.15 vs − 0.7 g/dL	Concordant (+)
Parsaclisib (phase 2)[23]	OL SA, mixed AIHA	25	FACIT-F	W6 + 7.6 (SD 10.4); sustained W12	W12 Hb 10.9 g/dL (≥ 2 in 43.5%)	Concordant (+)
Fostamatinib (FORWARD, phase 3)[21]	RCT DB, wAIHA	90	FACIT-F	+ 2.9 vs + 1.9 PBO; post-hoc + 7.0 vs + 0.7	Hb increase + 1.8 vs + 1.85 (overall)	Concordant (−)

Abbreviations: BL, baseline; DB, double-blind; Hb, hemoglobin; LASA, Linear Analog Self-Assessment; LT, long-term; LV, last visit; OL, open-label; OLE, open-label extension; PBO, placebo; pts, points; SA, single-arm; TAT, treatment assessment time.

Table 2
PROM and biomarker results in ITP studies

Drug (study)	Design	N	PROM	PROM result	PLT response	Concordance
Eltrombopag (RAISE, p3)[26]	RCT DB	197	SF-36v2, FACIT-F, FACT-Th6, MEI-SF	5/8 SF-36 domains sig; FACIT-F + 1.6 vs − 0.8 (NS)	79% vs 28%	Discordant-PROM
Eltrombopag (EXTEND, OLE)[27]	OL long-term	302	FACIT-F, SF-36	FACIT-F + 1.6 (0.6–2.5) for PLT ≥ 50 vs < 50	85.8%	Concordant (+)
Eltrombopag (CITE / TAPER)[28,29]	OBS / Phase 2	231 / 105	FACIT-F, SF-36	Sustained modest gains (M12 + 7.9)	CITE 89.7%; TAPER SRoT 30.5%	Concordant (+)
Romiplostim (vs SOC, p3)[30]	RCT OL	234	ITP-PAQ	7/10 scales sig; Fatigue + 11.2 vs + 9.5 (NS)	89% vs 70%	Discordant-PROM (fatigue)
Avatrombopag (ADOPT, p4)[31]	OBS	199	FACIT-F	+ 2.5 (paired n = 60 + 12m)	80%	Discordant-PROM (fatigue)
Mycophenolate (FLIGHT, p3)[32]	RCT OL	120	FACIT-F, SF-36, FACT-Th6	FACIT-F − 3.3 (− 6.6 to − 0.04); SF-36 PF worse	Superior	Discordant-PROM (harm)
Efgartigimod IV (ADVANCE IV, p3)[35]	RCT DB	131	FACIT-F, FACT-Th6, SF-36	FACIT-F + 0.71 vs + 0.97 (NS); FACT-Th6 and SF-36 MCS improved	22% vs 5%	Discordant-PROM
Efgartigimod SC (ADVANCE SC, p3)[36]	RCT DB	207	FACIT-F, FACT-Th6, SF-36	Failed primary; PROMs null	13.7% vs 16.2%	Concordant (–)
Rilzabrutinib (LUNA3, p3)[33]	RCT DB	202	ITP-PAQ	Item 10 + 12.0 (p = 0.0003) at W25	23%	Discordant-biomarker

Abbreviations: CMPR, clinically meaningful platelet response; DB, double-blind; DXM, dexamethasone; EQ-VAS, EuroQol visual analogue scale; FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue; FACT-Th6, Functional Assessment of Cancer Therapy–Thrombocytopenia 6-item; HD, high-dose; HRQoL, health-related quality of life; ITP, immune thrombocytopenia; ITP-PAQ, ITP Patient Assessment Questionnaire; IV, intravenous; M12, month 12; MCS, mental component summary; MEI-SF, Motivation and Energy Inventory–Short Form; MFI-20, Multidimensional Fatigue Inventory-20; MID, minimal important difference; myOpp, myOpportunITy; NS, not significant; OBS, observational; OL, open-label; OLE, open-label extension; p2/p3/p4, phase 2/3/4; PBO, placebo; PF, physical functioning; PLT, platelet; PROM, patient-reported outcome measure; PROMIS-F, PROMIS–Fatigue; RCT, randomized controlled trial; SA, single-arm; SC, subcutaneous; SD, standard deviation; SF-12/SF-36(v2), 12-/36-Item Short Form Health Survey (version 2); SOC, standard of care; SRoT, sustained response off treatment; term., terminated; W, week.

Drug (study)	Design	N	PROM	PROM result	PLT response	Concordance
Rilzabrutinib (LUNA2, p2b)[44]	OL SA	26	ITP-PAQ, EQ-VAS	MID reached (HRQoL + 13; fatigue/sleep + 13)	35% durable	Concordant (+)
Ianalumab (VAYHIT2, p3)[34]	RCT DB	152	PROMIS-F, ITP-PAQ	ITP-PAQ + 22.1 vs + 11.2; PROMIS-F favored	73% vs 48%	Concordant (+)
Iptacopan (p2 basket, ITP)[18]	OL SA	9	FACIT-F	–3 (no benefit)	No	Concordant (–)
Rozanolixizumab (myOpportunITy1/2/3)[40]	RCT DB (term.) + OLE	33/30/43	ITP-PAQ	Symptoms Δ, mean (SD): +5.5 (9.2) / +4.2 (12.9) vs PBO + 6.9 (13.8) / −0.5 (17.0) (myOpp1 / 2)	CMPR: 19% vs 0% PBO	Concordant (+)
Cevidoplenib (p2)[45]	RCT DB	60	SF-12	MCS + 4.9 (200 mg) vs + 1.6 (PBO)	46% (200 mg), 64% (400 mg) vs 33%	Mixed
Diacerein + eltrombopag (p2)[37]	RCT OL	102	ITP-PAQ	Fatigue p = 0.0004; >MID (combination)	44% vs 13%	Concordant (+)
Rituximab (single- vs low-dose)[41]	RCT	88	ITP-PAQ	Single-dose > low-dose (psych, QoL)	Comparable (64 vs 67%)	Discordant (PROM-only)
Caffeic acid + HD-DXM (phase 2)[38]	RCT DB	214	ITP-PAQ	Fatigue p = 0.0002 (W12); >MID	56.5% vs 29.2%	Concordant (+)
Oseltamivir + DXM (p2)[39]	RCT OL	90	ITP-PAQ	Symptoms > MID; fatigue NS (p = 0.059)	53% vs 30%	Discordant-PROM (fatigue)

Abbreviations: CMPR, clinically meaningful platelet response; DB, double-blind; DXM, dexamethasone; EQ-VAS, EuroQol visual analogue scale; FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue; FACT-Th6, Functional Assessment of Cancer Therapy–Thrombocytopenia 6-item; HD, high-dose; HRQoL, health-related quality of life; ITP, immune thrombocytopenia; ITP-PAQ, ITP Patient Assessment Questionnaire; IV, intravenous; M12, month 12; MCS, mental component summary; MEI-SF, Motivation and Energy Inventory–Short Form; MFI-20, Multidimensional Fatigue Inventory-20; MID, minimal important difference; myOpp, myOpportunITy; NS, not significant; OBS, observational; OL, open-label; OLE, open-label extension; p2/p3/p4, phase 2/3/4; PBO, placebo; PF, physical functioning; PLT, platelet; PROM, patient-reported outcome measure; PROMIS-F, PROMIS–Fatigue; RCT, randomized controlled trial; SA, single-arm; SC, subcutaneous; SD, standard deviation; SF-12/SF-36(v2), 12-/36-Item Short Form Health Survey (version 2); SOC, standard of care; SRoT, sustained response off treatment; term., terminated; W, week.

Drug (study)	Design	N	PROM	PROM result	PLT response	Concordance
Daratumumab (DART, p2)[42]	OL SA	21	SF-36, MFI-20	Responders > MID in 4 SF-36 domains	48%	Concordant (+)
Baricitinib (BAITP, p2)[43]	OL SA	35	ITP-PAQ	≥MID: symptoms, fatigue, QoL	57%	Concordant (+)
Splenectomy[46]	OBS	69 / 89	SF-36	Several domains worse than medical therapy	Durable remission	Discordant (PLT w/o QoL)

Abbreviations: CMPR, clinically meaningful platelet response; DB, double-blind; DXM, dexamethasone; EQ-VAS, EuroQol visual analogue scale; FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue; FACT-Th6, Functional Assessment of Cancer Therapy–Thrombocytopenia 6-item; HD, high-dose; HRQoL, health-related quality of life; ITP, immune thrombocytopenia; ITP-PAQ, ITP Patient Assessment Questionnaire; IV, intravenous; M12, month 12; MCS, mental component summary; MEI-SF, Motivation and Energy Inventory–Short Form; MFI-20, Multidimensional Fatigue Inventory-20; MID, minimal important difference; myOpp, myOpportunITy; NS, not significant; OBS, observational; OL, open-label; OLE, open-label extension; p2/p3/p4, phase 2/3/4; PBO, placebo; PF, physical functioning; PLT, platelet; PROM, patient-reported outcome measure; PROMIS-F, PROMIS–Fatigue; RCT, randomized controlled trial; SA, single-arm; SC, subcutaneous; SD, standard deviation; SF-12/SF-36(v2), 12-/36-Item Short Form Health Survey (version 2); SOC, standard of care; SRoT, sustained response off treatment; term., terminated; W, week.

Results

Study selection and characteristics

After title/abstract screening of 1533 AIHA and 2204 ITP records and full-text assessment of 100 and 182 reports, respectively, 32 AIHA reports (10 trials/datasets) and 43 ITP reports (24 trials/datasets) were included (Fig. 1). AIHA evidence comprised 8 single-arm treatment cohorts, placebo-controlled RCTs, and registry cohorts spanning CAD (sutimlimab, pegcetacoplan), wAIHA (rilzabrutinib, sovleplenib, fostamatinib), and mixed AIHA (parsaclisib). ITP evidence comprised placebo- and standard-of-care–controlled RCTs, open-label extensions, active-comparator and add-on RCTs, and observational cohorts across TPO-RAs, Fc/FcRn- and complement-directed agents, kinase inhibitors, and immunomodulators. A complete study-by-study inventory is provided in Supplementary Results.

PROM selection was heterogeneous across studies. In AIHA, all studies reported the FACIT-Fatigue scale. ITP studies used a broader array of instruments; most reported FACIT-Fatigue (8 arms) or the ITP-PAQ Fatigue domain (6 arms), or both. Additional instruments (EQ-5D-5L, EQ-VAS, SF-12 PCS/MCS, PGIS, PGIC) consistently supported FACIT-Fatigue results and are detailed in the Supplementary Materials.

PROMs in AIHA studies

Table 1 summarizes PROM data from CAD and wAIHA trials. All AIHA studies used the FACIT-Fatigue scale, a 13-item instrument scored 0–52 (higher = less fatigue; CIC ≥ 5 points).[8] Generic HRQoL was assessed with the SF-12 (PCS/MCS), EQ-5D, and EQ-VAS.

In the open-label, single-arm CARDINAL study of sutimlimab in recently transfused CAD,[11] FACIT-Fatigue improved by an LS mean of 10.9 points (95% CI [8.0–13.7]), with 90% achieving a clinically meaningful response; the gain was sustained at + 11.7 points at week 135 of the extension,[12] with concordant SF-12 and PGIC improvements and reversal toward baseline during the 9-week washout.

In the randomized, placebo-controlled CADENZA trial,[13,14] sutimlimab improved FACIT-Fatigue by an LS mean of 10.8 versus 1.9 points for placebo (difference 8.9 points; $p < 0.001$), with supportive SF-12 PCS and EQ-VAS gains; placebo-to-sutimlimab switchers improved rapidly in the extension,[15] and at the end of the 9-week washout the mean change fell to − 1.4 points (> 100% of the on-treatment benefit lost) as Hb returned to baseline.

In the single-arm phase 2 PLAUDIT study, pegcetacoplan[16] (n = 13) produced a median FACIT-Fatigue change of + 10.5 points at week 8. In the placebo-controlled phase 3 CASCADE trial,[17] pegcetacoplan increased Hb more than placebo (between-group + 1.49 g/dL) but the between-group FACIT-Fatigue difference was small (+ 0.93 points) because the placebo arm also improved (+ 8.8 points); placebo-to-pegcetacoplan switchers improved further in the extension.

In a phase 2 single-arm basket study of the alternative-pathway inhibitor iptacopan,[18] the CAD cohort (n = 10) achieved a mean FACIT-Fatigue increase of 8.8 points (range 2.0–16.0) at week 12.

In wAIHA, fatigue was again assessed predominantly by FACIT-Fatigue. The phase 2b LUMINA-2 study of the BTK inhibitor rilzabrutinib[19,20] improved mean FACIT-Fatigue from 30 to 37 at week 24, with a fatigue response in 64.3% of hemoglobin responders and, notably, 25% of hemoglobin non-responders, the latter correlating with reductions in inflammatory cytokines ($r = -0.65$ to -0.77). The SYK inhibitor fostamatinib (FORWARD)[21] showed modest separation from placebo overall (+ 2.9 vs + 1.9) but larger benefit in a post-hoc wAIHA-restricted analysis (+ 7 vs + 0.7). The SYK inhibitor sovleplenib (ESLIM-02)[22] improved fatigue on a non-standard 0–160 scale (pooled only after harmonization, as a sensitivity), and the PI3Kδ inhibitor parsaclisib[23] improved FACIT-Fatigue by 7.6 points by week 6 in a mixed-AIHA phase 2 study.

Three placebo-controlled AIHA RCTs reported FACIT-Fatigue between-group differences: CADENZA (sutimlimab, CAD; MD + 8.9), FORWARD (fostamatinib, wAIHA; MD + 1.0 prespecified), and CASCADE (pegcetacoplan, CAD; MD + 0.93). The pooled MD was + 4.2 points (95% CI [− 7.6–16.1]; k = 3; Hartung–Knapp; $I^2 = 67\%$), with a prediction interval (− 18.2 to 26.6) spanning benefit and harm. The confidence interval crossed zero, so the between-group RCT evidence is weaker than the single-arm change scores suggest; adding the harmonized sovleplenib wAIHA trial as a sensitivity did not change this.

Across the 8 single-arm AIHA treatment cohorts (n = 166), the pooled mean FACIT-Fatigue CFB was 9.2 points (95% CI [7.9–10.5]; $P < 0.0001$), exceeding the CIC of 3 points, with no heterogeneity ($I^2 = 0\%$) and a prediction interval (7.3–10.9) entirely above the CIC (Fig. 2); leave-one-out estimates ranged 8.5–9.5. Represented classes included complement inhibitors (sutimlimab, pegcetacoplan, iptacopan), rilzabrutinib, and parsaclisib. The pooled placebo/control arms of the controlled trials changed by only + 2.1 points (95% CI [− 1.6–5.8]). By subtype, the pooled CFB was 9.9 points (CAD; k = 5) versus 7.3 points (wAIHA; k = 2); the 2.6-point difference was not significant ($p = 0.21$), limited by only 2 wAIHA studies.

PROMs in ITP studies

Table 2 details ITP PROM results, which reveal a complex relationship between platelet counts and quality of life. FACIT-Fatigue was used in 5 studies and the PROMIS-Fatigue short form (essentially FACIT-Fatigue on a T-score metric) in the VAYHIT2 trial of ianalumab. The SF-36 was used in 3 studies, the disease-specific ITP-PAQ (10 scales, scored 0–100)[24] in 3, and the FACT-Th6 bleeding-anxiety measure[25] in 3.

TPO-RAs showed unclear fatigue results. In the RAISE trial of eltrombopag,[26] 5 of 8 SF-36v2 domains and FACT-Th6 (+ 1.5; p = 0.004) improved significantly, but FACIT-Fatigue did not (+ 1.6 vs − 0.8; p = 0.08); the EXTEND, CITE, and TAPER cohorts[27–29] showed only small, sustained FACIT-Fatigue gains. The open-label romiplostim study[30] improved 7 of 10 ITP-PAQ scales but not the fatigue scale (+ 11.2 vs + 9.5; p = 0.34). The phase 4 real-world ADOPT study of avatrombopag[31] (n = 199) showed a median FACIT-Fatigue improvement of 2.5 points, below the 3-point CIC, with concordant ITP-PAQ domain gains.

The open-label FLIGHT trial of mycophenolate mofetil[32] improved platelets but worsened SF-36 Physical Functioning (MD − 5.9). Conversely, the phase 3 LUNA3 study of rilzabrutinib[33] improved ITP-PAQ physical fatigue (LS MD + 12.0 at week 25; p = 0.0003), with meaningful gains (> 8 points) in psychological health, HRQoL, and symptoms. Ianalumab (VAYHIT2)[34] produced greater fatigue reduction than placebo (PROMIS-Fatigue T-score − 7.7 vs − 3.6; ITP-PAQ Fatigue + 22.1 vs + 11.2).

In the ADVANCE IV trial of the FcRn inhibitor efgartigimod,[35] SF-36 MCS and FACT-Th6 improved but FACIT-Fatigue did not (LS mean 0.708 vs 0.968); the subcutaneous formulation (ADVANCE SC)[36] missed its platelet endpoint and showed no PROM benefit. In the ITP cohort of the iptacopan basket study,28 FACIT-Fatigue declined (34.4 to 22.7), consistent with the absence of platelet response.

Add-on RCTs pairing an immunomodulatory agent with standard therapy reported significant ITP-PAQ fatigue-domain gains (diacerein plus eltrombopag,[37] p = 0.0004; caffeic acid plus high-dose dexamethasone,[38] p = 0.0002), whereas oseltamivir plus dexamethasone improved symptoms but not fatigue[39] (p = 0.059). Rozanolixizumab (myOpportunITy)[40] was underpowered for PROMs; single- versus low-dose rituximab[41] favored single dosing; daratumumab (DART),[42] baricitinib (BAITP),[43] and rilzabrutinib (LUNA2)[44] reported meaningful gains in responders; the SYK inhibitor cevidoplenib numerically improved SF-12 MCS only at the 200-mg dose;[45] and in two splenectomy cohorts,[46] HRQoL was no better than medical therapy.

The pooled between-group FACIT-Fatigue MD across 5 ITP RCTs (RAISE, FLIGHT, ADVANCE IV, ADVANCE SC, VAYHIT2) was + 0.6 points (95% CI [− 3.2–4.4]; p = 0.70; I^2 = 74%; Hartung–Knapp), below the 3-point CIC, with a prediction interval (− 7.4 to + 8.5) and effects ranging from negative (MMF FLIGHT; MD − 3.3) to positive (ianalumab VAYHIT2; crosswalked MD 5.2). Excluding the crosswalked VAYHIT2 data yielded a pooled MD of − 0.2 (95% CI [− 4.0–3.5]; k = 4), confirming harmonization did not drive the null.

In contrast, the ITP-PAQ Fatigue domain showed a pooled between-group MD of + 8.6 points (romiplostim, rilzabrutinib LUNA3, ianalumab VAYHIT2) but, under Hartung–Knapp, did not reach significance (95% CI [− 5.2–22.4]; p = 0.11; k = 3; I^2 = 46%); the wide prediction interval (− 12.3 to 29.5) reflected divergent effects between romiplostim (MD 1.7, non-significant) and the newer agents rilzabrutinib and ianalumab (MDs 12.0 and 10.9).

Biomarkers versus PROMs

A standardized comparison of disease-activity biomarkers and PROM effects showed limited and variable concordance. Across the 8 single-arm AIHA cohorts, hemoglobin and FACIT-Fatigue changes were positively associated (random-effects meta-regression β = +3.2 points per g/dL; 95% CI [0.5–5.9]; p = 0.03), and washout data from CADENZA Part B showed that essentially all of the on-treatment FACIT-Fatigue gain was lost as hemoglobin returned to baseline during the 9-week treatment-free period, consistent with reversibility of the hemolysis–fatigue link. Concordance was nonetheless not uniform even within a single pathway: in CAD, pegcetacoplan (CASCADE) produced a large between-group hemoglobin effect with only a small FACIT-Fatigue effect, whereas sutimlimab (CADENZA) showed concordant effects. In ITP, platelet responses were large and consistent, yet the pooled between-group FACIT-Fatigue difference was null (+ 0.6 points; 95% CI − 3.2 to 4.4; I^2 = 74%) and the ITP-PAQ Fatigue difference, though larger, was non-significant (+ 8.6 points; 95% CI − 5.2 to 22.4); conversely, rilzabrutinib (LUNA3) showed the opposite dissociation, with an ITP-PAQ Fatigue improvement of 12 points despite a 23% platelet response rate. Concordance was thus agent- and context-dependent rather than a fixed property of either disease. Full meta-regression, subgroup, correlation, and washout results are provided in Supplementary Results.

Discussion

In the era of rapidly evolving treatment options for AIHAs and ITP, outcomes beyond the level of Hb and PLT should be considered while managing patients. The importance of fatigue and other PROs is emerging, and their assessment has been implemented in clinical trials with novel drugs. However, this is like “new evidence with limited history”, since there is a general lack of data concerning the impact and dynamics of PROMs upon therapy with traditional immunosuppressive therapies, such as steroids and rituximab, not to mention splenectomy or chemotherapy. Additionally, we still miss disease-specific tools to quickly and efficiently assess PROMs in the real world.

This systematic review and meta-analysis describes patient-reported outcomes and their relationship with biomarkers across treatments for autoimmune cytopenias. In AIHA, the FACIT-Fatigue improvement in single-arm studies was large (+ 9.2 points) and homogeneous across eight treatment arms of five drug classes; hemoglobin change was positively associated with fatigue change (+ 3.2 points per g/dL), and the Hb–FACIT correlation was strong and homogeneous (r = 0.64; I^2 = 0%). These associations are consistent with a hemoglobin–fatigue link in CAD. The washout data from CADENZA Part B, in which both hemoglobin and FACIT-Fatigue scores returned to baseline upon cessation of treatment, remain a supportive, though uncontrolled, line of evidence for this link. However, several factors beyond Hb levels may influence fatigue perception. For instance, in the pegcetacoplan phase 3 CASCADE CAD trial, hemoglobin separated from placebo while fatigue did not, because the placebo arm improved substantially, possibly due to seasonal cycles that characterize the disease. Similarly, in the LUMINA-2 trial, rilzabrutinib improved the FACIT-Fatigue score even in patients who did not meet the endpoint for Hb response. Interestingly, FACIT-Fatigue correlated negatively with IL-10 levels (r = − 0.65), possibly supporting a role for chronic inflammation in determining fatigue in wAIHA patients.

A greater fatigue improvement after treatment occurred in CAD compared with wAIHA (pooled FACIT-Fatigue CFB of 9.9 points vs. 7.3 points, respectively). It might be hypothesized that fatigue is mainly secondary to anemia and complement-mediated inflammatory activation in CAD, in keeping with reductions in several proinflammatory and immunoregulatory cytokines after treatment with sutimlimab. On the other hand, wAIHA seems to have a more complex pathogenesis, where fatigue might be more multifactorial and therefore less easy to target. In addition, the large use of corticosteroids may still impact PROMs even when hematologic response is achieved.

The ITP results present an even more complex picture with high heterogeneity. Discordant responses between PLT counts and FACIT-Fatigue were observed across TPO-RAs (eltrombopag), immunosuppressants (MMF), and FcRn inhibitors (efgartigimod), suggesting that the PLT count–fatigue dissociation reflects ITP pathophysiology rather than a class-specific pharmacological limitation. Nonetheless, the FACIT-Fatigue scale likely lacks sensitivity to the fatigue experience specific to ITP, as it measures global fatigue severity but does not capture the psychological and behavioral contributors, such as bleeding anxiety, activity avoidance, and hypervigilance regarding bruising, that constitute a major component of ITP functional impairment. Consistent with this broader symptom burden, up to 59% of patients with chronic ITP exhibit clinically important cognitive impairment, which is comparable in magnitude to mild traumatic brain injury and correlates with fatigue and age but not with platelet count or corticosteroid use.[47] Nationwide registry data further link ITP to a markedly increased burden of mental health events, including a 3.5 times higher risk of any mental health event and of depression in the first year, together with greater peri-diagnostic use of opioids, antidepressants, and benzodiazepines than in the general population.[48] The disease-specific ITP-PAQ Fatigue domain shows greater ability to estimate fatigue (MD + 8.6 points), which is consistent with disease-specific instruments being more sensitive than generic fatigue measures in ITP, although prospective validation remains needed. Moreover, the contribution of treatment-related side effects, particularly with corticosteroids and immunosuppressants, may counterbalance the benefits of PLT improvement on fatigue, explaining the negative between-group difference observed with MMF in the FLIGHT trial. Additionally, fatigue in ITP may be partially driven by immune dysregulation and low-grade chronic inflammation, producing a persistent symptom burden even after hematologic correction. The LUNA3 result illustrates this dissociation: the ITP-PAQ Fatigue score improved by 12 points despite a PLT response rate of only 23%. As an upstream immunomodulator, the BTK inhibitor rilzabrutinib may attenuate inflammatory cytokine activity and influence immune-mediated fatigue pathways independently of hematologic response. The I-WISh survey, in which 41% of patients ranked increasing energy as a top treatment goal[6], supports the employment of ITP-specific PROMs as primary endpoints in future prospective studies. Although PROM instruments are discussed descriptively, we did not perform a formal COSMIN evaluation of their measurement properties. Therefore, conclusions regarding comparative instrument performance should be interpreted cautiously.

Our analysis highlights the critical importance of instrument selection in autoimmune cytopenia trials. In AIHA, the FACIT-Fatigue performed consistently well, likely because fatigue is the dominant and most directly anemia-linked symptom. However, hemolysis-specific symptoms such as jaundice, dark urine, and acrocyanosis remain uncaptured by available instruments. Dyspnea is a further under-recognized manifestation of wAIHA: in a qualitative interview study, all patients described exertional dyspnea with a substantial impact on daily functioning, and the FACIT-Dyspnea 10-item short form showed content validity in this population, supporting its evaluation as a complementary patient-centered endpoint.[49] In ITP, the divergent results between FACIT-Fatigue and ITP-PAQ underscore that generic fatigue measures may underestimate treatment benefit when disease burden encompasses psychological and behavioral dimensions. This also highlights the general lack of awareness of the need for social and psychological support of ITP patients in the clinical routine.

This meta-analysis is limited by the small number of studies in each analytic pool, which reduces the statistical power for quantifying heterogeneity, conducting subgroup comparisons, and assessing publication bias. Furthermore, single-arm studies constituted the majority of the AIHA pool, limiting causal inference despite supportive evidence from RCTs, meta-regression, and washout reversal. Additionally, heterogeneity in treatment timepoints (6–135 weeks) may introduce temporal confounding, as some PROMs may not have reached steady

state by the assessment window. Finally, GRADE certainty was LOW to VERY LOW, and conclusions are correspondingly cautious and hypothesis-generating.

In conclusion, correcting the laboratory abnormalities (i.e., Hb and platelets) is necessary but not sufficient for treating patients with autoimmune cytopenias. This meta-analysis indicates that, in AIHA and particularly CAD, Hb improvement is associated with reduced fatigue. However, targeting chronic inflammation with novel drugs might induce significant and perceived benefit beyond hematologic improvement even in “non-responders”. In ITP, platelet count improvement alone does not necessarily translate into fatigue reduction, reflecting the multifactorial nature of ITP-related symptoms and advocating for a more holistic approach. The era of targeted agents in autoimmune cytopenias demands a parallel evolution in the measurement of treatment success, shifting from laboratory surrogates alone to the integration of disease-specific, psychometrically validated PROMs that reflect patient-relevant outcomes.

Declarations

Competing Interests

G.L.P. received lecture fess or congress support from Alexion Pharmaceuticals, Avanzanite Biosciences BV, Novartis, Recordati Rare Diseases, and Roche. E.N.O. reports receiving consultancy/speaker bureau fees from Alexion Pharmaceuticals, Bristol Myers Squibb, Daiichi Sankyo, Janssen, Novartis, Pfizer, Ryvu Therapeutics, Sanofi, Sobi, and Syros Pharmaceuticals; and patents and royalties from Bristol Myers Squibb, Halia Therapeutics, and Ryvu Therapeutics. B.F. received consultancy and speaker's bureau from Alexion, AstraZeneca, Janssen, Novartis, Recordati, Roche, and Sanofi.

Data-sharing statement

This systematic review and meta-analysis aggregates data from previously published studies and publicly available clinical-trial reports and registries. All included studies are cited in the manuscript. PRISMA 2020 checklist, search strategy and the list of excluded studies are reported as Supplementary Material The study-level data extracted from the included reports and the R script used for the meta-analysis are available from the corresponding author upon reasonable request.

Funding:

Italian Ministry of Health, Current Research

Author Contribution

G.L.P. and B.F. conceived and designed the study. G.L.P. and B.F. independently performed the literature search, study selection, and data extraction. Disagreements were resolved by consensus. G.L.P. performed the statistical analysis and drafted the manuscript. E.N.O. and B.F. provided clinical and methodological expertise and critically revised the manuscript. All authors had access to the study data, interpreted the results, and reviewed and approved the final manuscript.

Acknowledgement

G.L.P. acknowledges financial support from the Università degli Studi di Milano through the PhD program in Translational Medicine.

Data Availability

This systematic review and meta-analysis aggregates data from previously published studies and publicly available clinical-trial reports and registries. All included studies are cited in the manuscript. PRISMA 2020 checklist, search strategy and the list of excluded studies are reported as Supplementary Material The study-level data extracted from the included reports and the R script used for the meta-analysis are available from the corresponding author upon reasonable request.

References

1. US Food and Drug Administration (2009) Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims. Fed Regist. :65132
2. Berentsen S, Fattizzo B, Barcellini W (2023) The choice of new treatments in autoimmune hemolytic anemia: how to pick from the basket? Front Immunol 14:1180509
3. Jäger U, Barcellini W, Broome CM, Gertz MA, Hill A, Hill QA, Jilma B, Kuter DJ, Michel M, Montillo M, Röth A (2020) Diagnosis and treatment of autoimmune hemolytic anemia in adults: Recommendations from the First International Consensus Meeting. Blood Rev 41:100648
4. Neunert C, Terrell DR, Arnold DM, Buchanan G, Cines DB, Cooper N, Cuker A, Despotovic JM, George JN, Grace RF, Kühne T (2019) American Society of Hematology 2019 guidelines for immune thrombocytopenia. Blood Adv 3(23):3829–3866
5. Provan D, Arnold DM, Bussel JB, Chong BH, Cooper N, Gernsheimer T, Ghanima W, Godeau B, González-López TJ, Grainger J, Hou M (2019) Updated international consensus report on the investigation and management of primary immune thrombocytopenia. Blood Adv 3(22):3780–3817
6. Cooper N, Kruse A, Kruse C, Watson S, Morgan M, Provan D, Ghanima W, Arnold DM, Tomiyama Y, Santoro C, Michel M (2021) Immune thrombocytopenia (ITP) World Impact Survey (I-WISh): impact of ITP on health-related quality of life. Am J Hematol 96(2):199–207
7. Mokkink LB, Terwee CB, Patrick DL, Alonso J, Stratford PW, Knol DL, Bouter LM, De Vet HC (2010) The COSMIN checklist for assessing the methodological quality of studies on measurement properties of health status measurement instruments: an international Delphi study. Qual Life Res 19(4):539–549
8. Cella D, Hill QA, Karaouni A, Joly F, Sourdille T, Shafer F, Wardęcki M, Kosinski M, Röth A (2025) FACIT-Fatigue scale in patients with cold agglutinin disease: psychometric validation and estimation of clinically meaningful change. Front Hematol 4:1490130
9. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R (2021) The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. ;372
10. Cella D, Johansson P, Ueda Y, Tomazos I, Gustovic P, Wang A, Patel AS, Schrezenmeier H (2023) Clinically important change for the FACIT-Fatigue scale in paroxysmal nocturnal hemoglobinuria: a derivation from

international PNH registry patient data. J patient-reported outcomes 7(1):63

11. Röth A, Barcellini W, D'Sa S, Miyakawa Y, Broome CM, Michel M, Kuter DJ, Jilma B, Tvedt TH, Fruebis J, Jiang X (2021) Sutimlimab in cold agglutinin disease. N Engl J Med 384(14):1323–1334
12. Röth A, Broome CM, Barcellini W, Tvedt TH, Miyakawa Y, D'Sa S, Cella D, Bozzi S, Jayawardene D, Yoo R, Shafer F (2023) Long-term sutimlimab improves quality of life for patients with cold agglutinin disease: CARDINAL 2-year follow-up. Blood Adv 7(19):5890–5897
13. Röth A, Berentsen S, Barcellini W, D'Sa S, Jilma B, Michel M, Weitz IC, Yamaguchi M, Nishimura JI, Vos JM, Storek M (2022) Sutimlimab in patients with cold agglutinin disease: results of the randomized placebo-controlled phase 3 CADENZA trial. Blood J Am Soc Hematol 140(9):980–991
14. Röth A, Broome CM, Barcellini W, Jilma B, Hill QA, Cella D, Tvedt TH, Yamaguchi M, Lee M, Shafer F, Wardęcki M (2023) Sutimlimab provides clinically meaningful improvements in patient-reported outcomes in patients with cold agglutinin disease: Results from the randomised, placebo-controlled, Phase 3 CADENZA study. Eur J Haematol 110(3):280–288
15. Röth A, Berentsen S, Barcellini W, D'Sa S, Jilma B, Michel M, Weitz IC, Yamaguchi M, Nishimura JI, Vos JM, Cid J (2024) Long-term efficacy and safety of continued complement C1s inhibition with sutimlimab in cold agglutinin disease: CADENZA study Part B. EClinicalMedicine. ;74
16. Roman E, Fattizzo B, Shum M, Hanna W, Lentz SR, Araujo SS, Al-Adhami M, Grossi FV, Gertz MA (2025) Safety and efficacy of pegcetacoplan treatment for cold agglutinin disease and warm antibody autoimmune hemolytic anemia. Blood 145(4):397–408
17. A study to evaluate the efficacy and safety of pegcetacoplan in patients with cold agglutinin disease (CAD) (CASCADE). ClinicalTrials.gov identifier: NCT05096403. https://clinicaltrials.gov/study/NCT05096403
18. Röth A, Barcellini W, Ademokun C, Jang J, Lozano ML, Ferreiras DV, Pascual-Izquierdo C, Chitnis S, Matviykiv S, Vitaliti A, Chen C (2026) Iptacopan for Immune Thrombocytopenia and Cold Agglutinin Disease: A Global Phase 2 Basket Clinical Trial. Am J Hematol 101(2):242–254
19. Cooper N, Kuter DJ, Frederiksen H, Han B, Chen F, Barcellini W, Cid J, Broome CM, Vara M, Mazumder A, Lucchesi A (2024) Part a efficacy and safety of oral bruton tyrosine kinase inhibitor (BTKi) rilzabrutinib in patients with warm autoimmune hemolytic anemia (wAIHA): multicenter, open-label, phase 2b study. Blood 144:3836
20. Kuter D, Cooper N, Orsini M, Msihid J, Pollissard L, Cordoba M, Daak A, Wardecki M, Wang L, Fattizzo B (2025) Fatigue, hemoglobin, and inflammatory markers in warm autoimmune hemolytic anemia: analysis from a phase 2b trial of rilzabrutinib (LUMINA2). Blood 146(Suppl 1):1105
21. Kuter DJ, Piatek C, Röth A, Siddiqui A, Numerof RP, Dummer W, FORWARD Study Group (2024) Fostamatinib for warm antibody autoimmune hemolytic anemia: phase 3, randomized, double-blind, placebo-controlled, global study (FORWARD). Am J Hematol 99(1):79–87
22. Zhao X, Sun J, Zhang Z, Chen M, Gong T, He G, Li Y, Liu H, Li F, Li X, Zhou H (2025) Sovleplenib in patients with primary or secondary warm autoimmune haemolytic anaemia: results from phase 2 of a randomised, double-blind, placebo-controlled, phase 2/3 study. Lancet Haematol 12(2):e97–108
23. Barcellini W, Pane F, Patriarca A, Murakhovskaya I, Terriou L, DeSancho MT, Hanna WT, Leopold L, Rappold E, Szeto K, Wei S (2024) Parsaclisib for the treatment of primary autoimmune hemolytic anemia: Results from a phase 2, open-label study. Am J Hematol 99(12):2313–2320

24. Mathias SD, Bussel JB, George JN, McMillan R, Okano GJ, Nichol JL (2007) A disease-specific measure of health-related quality of life for use in adults with immune thrombocytopenic purpura: its development and validation. Health Qual Life Outcomes 5(1):11
25. Signorovitch J, Brainsky A, Grotzinger KM (2011) Validation of the FACIT-fatigue subscale, selected items from FACT-thrombocytopenia, and the SF-36v2 in patients with chronic immune thrombocytopenia. Qual Life Res 20(10):1737–1744
26. Cheng G, Saleh MN, Marcher C, Vasey S, Mayer B, Aivado M, Arning M, Stone NL, Bussel JB (2011) Eltrombopag for management of chronic immune thrombocytopenia (RAISE): a 6-month, randomised, phase 3 study. Lancet 377(9763):393–40224
27. Khelif A, Saleh MN, Salama A, Portella MD, Duh MS, Ivanova J, Grotzinger K, Roy AN, Bussel JB (2019) Changes in health-related quality of life with long-term eltrombopag treatment in adults with persistent/chronic immune thrombocytopenia: findings from the EXTEND study. Am J Hematol 94(2):200–208
28. Wong RS, Yavaşoğlu İ, Yassin MA, Tarkun P, Yoon SS, Wei X, Elghandour A, Angchaisuksiri P, Ozcan M, Yang R, Mattar M (2023) Eltrombopag in patients with chronic immune thrombocytopenia in Asia-Pacific, the Middle East, and Turkey: final analysis of CITE. Blood Adv 7(17):4773–4781
29. Cooper N, Ghanima W, Vianelli N, Valcárcel D, Yavaşoğlu İ, Melikyan A, Ruiz EY, Haenig J, Somenzi O, Lee J, Clark J (2024) Sustained response off-treatment in eltrombopag-treated adult patients with ITP who are refractory or relapsed after first-line steroids: primary, final, and ad-hoc analyses of the phase II TAPER trial. Am J Hematol 99(1):57–6728
30. Kuter DJ, Mathias SD, Rummel M, Mandanas R, Giagounidis AA, Wang X, Deuson RR (2012) Health-related quality of life in nonsplenectomized immune thrombocytopenia patients receiving romiplostim or medical standard of care. Am J Hematol 87(5):558–561
31. Mingot ME, Alvarez-Román MT, Lozano M, Miesbach W, Qureshi H, McDonald V, Zhang J, Garcia VC, Skuban N (2025) Patient-reported outcomes of avatrombopag for chronic immune thrombocytopenia: Interim analysis of the Phase 4 adopt study. Blood 146:6237
32. Bradbury CA, Pell J, Hill Q, Bagot C, Cooper N, Ingram J, Breheny K, Kandiyali R, Rayment R, Evans G, Talks K (2021) Mycophenolate mofetil for first-line treatment of immune thrombocytopenia. N Engl J Med 385(10):885–895
33. Kuter DJ, Ghanima W, Cooper N, Liebman HA, Zhang L, Hu Y, Miyakawa Y, Homenda W, Galindo LE, Basquiera AL, Tan CW (2025) Safety and efficacy of rilzabrutinib vs placebo in adults with immune thrombocytopenia: the phase 3 LUNA3 study. Blood 145(24):2914–2926
34. Cuker A, Stauch T, Cooper N, Al-Samkari H, Michel M, Ghanima W, Urban P, Fronczek J, Foster M, Weill M, Zhang L (2026) Ianalumab plus eltrombopag in immune thrombocytopenia. N Engl J Med 394(15):1503–1513
35. Broome CM, McDonald V, Miyakawa Y, Carpenedo M, Kuter DJ, Al-Samkari H, Bussel JB, Godar M, Ayguasanosa J, De Beuf K, Rodeghiero F (2023) Efficacy and safety of the neonatal Fc receptor inhibitor efgartigimod in adults with primary immune thrombocytopenia (ADVANCE IV): a multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 402(10413):1648–1659
36. Cooper N, Broome CM, Miyakawa Y, McDonald V, Al-Samkari H, Khelif A, Cataland SR, Barcellini W, Yang R, Mei H, Matthijssens F (2026) Efficacy and Safety of Subcutaneous Efgartigimod PH20 in Adults With Primary

Immune Thrombocytopenia (ADVANCE SC): A Multicenter, Randomized, Double-Blinded, Placebo-Controlled, Phase 3 Trial. Am J Hematol. Jul 1

37. Sun L, Huang X, Wang J, Yuan C, Zhao H, Li D, Xu R, Wang Y, Qin P, Shi Y, Peng J (2024) Eltrombopag plus diacerein vs eltrombopag in patients with ITP: a multicenter, randomized, open-label phase 2 trial. Blood 144(17):1791–1799
38. Wang R, Liu Y, Wang R, Cao J, Hao Y, Xiao T, Yu Z, Yu W, Chu X, Ran X, Zhu C (2025 Aug) Caffeic acid tablets plus high-dose dexamethasone versus placebo plus high-dose dexamethasone in patients with newly diagnosed immune thrombocytopenia: A multicenter, double-blind, randomized, controlled, phase 2 trial. Chin Med J 22:10–97
39. Sun L, Wang J, Shao L, Yuan C, Zhao H, Li D, Wang Z, Han P, Yu Y, Xu M, Zhao H (2021) Dexamethasone plus oseltamivir versus dexamethasone in treatment-naive primary immune thrombocytopenia: a multicentre, randomised, open-label, phase 2 trial. Lancet Haematol 8(4):e289–e298
40. A study to test the efficacy, safety, and tolerability of rozanolixizumab in adult participants with persistent or chronic primary immune thrombocytopenia (myOpportunITy). ClinicalTrials.gov identifiers: NCT04200456, NCT04224688, NCT04596995.
41. Ni X, Li D, Yuan C, Yu Y, Wang H, Wang L, Yu T, Qin P, Peng J, Hou M, Shi Y (2022) Single-dose versus low-dose rituximab in corticosteroid-resistant or relapsed ITP: A multicenter, randomized, controlled study. Am J Hematol 97(4):440–447
42. Tsykunova G, Holme PA, Tran HT, Frederiksen H, Tjønnfjord E, Munthe LA, Drivet E, Kared H, Sørvoll IH, Ahlen MT, Mahévas M (2026) Safety and efficacy of daratumumab in immune thrombocytopenia. Blood Adv 10(1):143–154
43. Zhao P, An ZY, Fu HX, Liu HX, Feng CJ, Huang QS, Wu J, Wu YJ, Yang LP, Qu QY, Chen YX (2024) Safety and efficacy of baricitinib in steroid-resistant or relapsed immune thrombocytopenia: An open-label pilot study. Am J Hematol 99(10):1951–1958
44. Cooper N, Jansen AG, Bird R, Mayer J, Sholzberg M, Tarantino MD, Garg M, Ypma PF, McDonald V, Percy C, Košťál M (2025) Efficacy and safety results with rilzabrutinib, an oral Bruton tyrosine kinase inhibitor, in patients with immune thrombocytopenia: phase 2 part B study. Am J Hematol 100(3):439–449
45. Study of oral SKI-O-703 SYK inhibitor, in patients with persistent and chronic immune thrombocytopenia (ITP). ClinicalTrials.gov identifier: NCT04056195. https://clinicaltrials.gov/study/NCT04056195
46. Caocci G, Efficace F, Mulas O, Cottone F, Maxia A, Costa A, Simula MP, Usala E, La Nasa G (2022) Health-related quality of life profile of patients with immune thrombocytopenia in the real life is impaired by splenectomy. Ann Hematol 101(4):749–754
47. Kuter DJ, Khan U, Maruff P, Daak A (2024) Cognitive impairment among patients with chronic immune thrombocytopenia. Br J Haematol 205(1):291–299
48. Mannering N, Hansen DL, Pottegård A, Andersen K, Frederiksen H (2024) Mental health and use of psychotropic prescription drugs in adult patients with primary immune thrombocytopenia: a nationwide population-based cohort study. Haematologica 109(9):2944
49. Kostikas M, Burrows K, Jones K, Woodburn R, Krol M, Cooper O, Daak A, Pollissard L, Bascle S, Maher J Investigating patients' experiences with dyspnea associated with warm antibody hemolytic anemia (wAIHA) and cognitive debriefing of the FACIT-dyspnea 10 item short form: A qualitative patient interview study

Figures

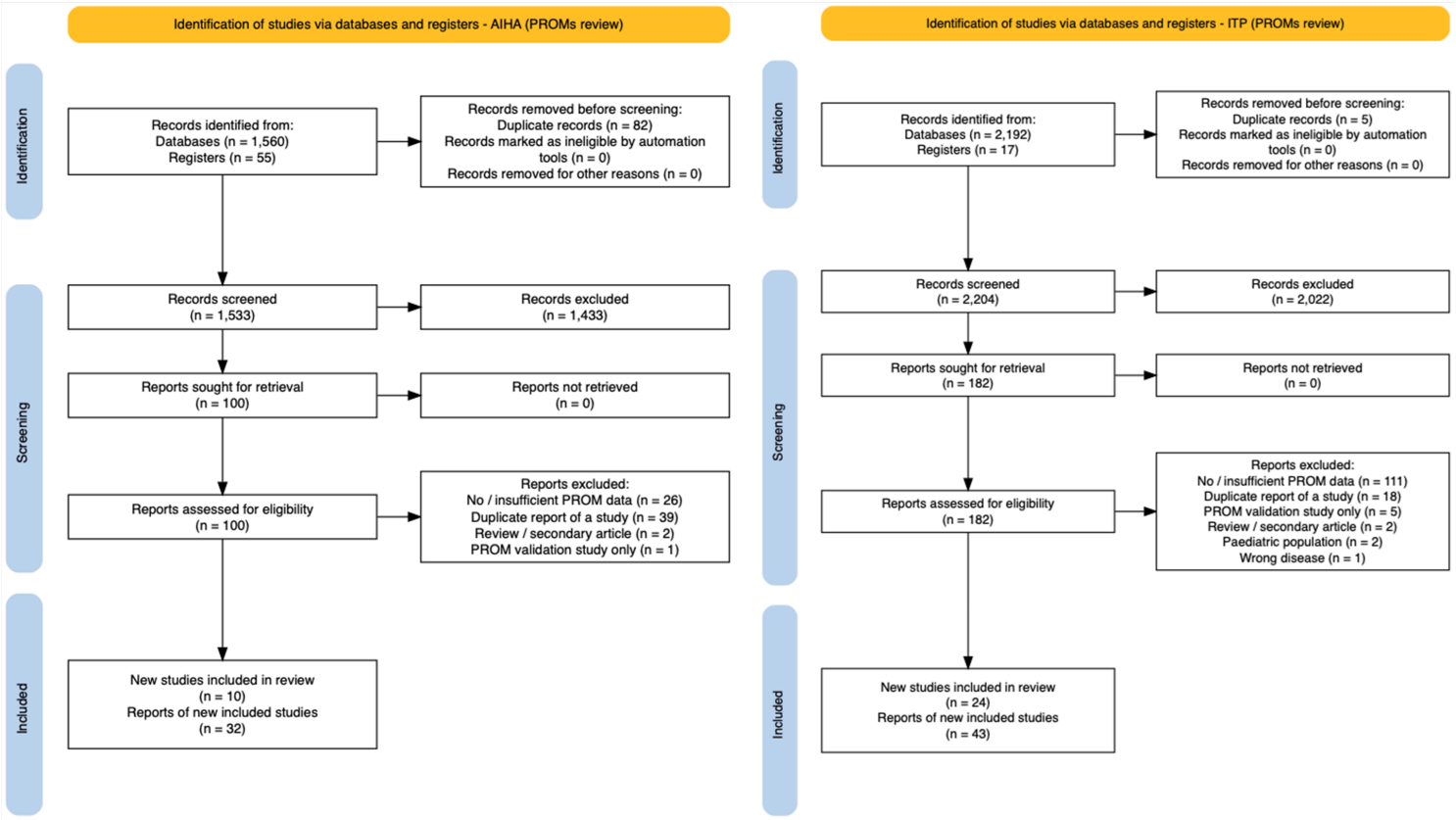

Figure 1

PRISMA 2020 flow diagram

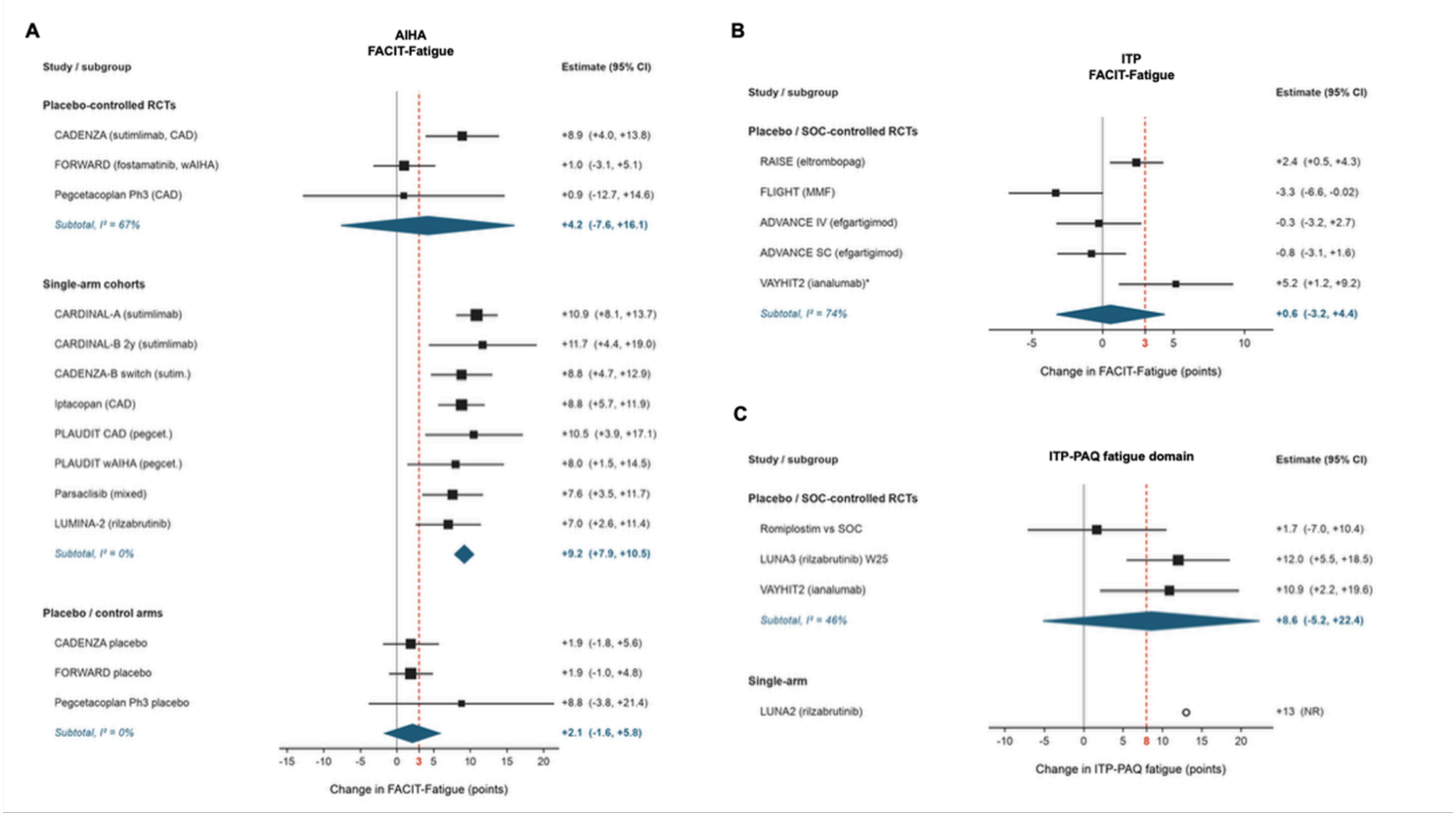

Figure 2

Forest plots of the FACIT-Fatigue changes in AIHA (A) and ITP (B), and of the ITP-PAQ changes (C)

Squares are individual-study estimates (area proportional to inverse-variance weight); horizontal lines are 95% confidence intervals (CIs); diamonds are stratum-specific random-effects pooled estimates (REML between-study variance, Knapp–Hartung CI). Strata: placebo-controlled RCTs (between-group mean difference, study treatment − control); single-arm cohorts (within-arm mean change from baseline); and the placebo/control arms of the RCTs (within-arm change). The red dashed lines mark the prespecified CIC thresholds. I^2 describes the between-study heterogeneity. LUNA2 is shown as the median change because no CI is available and is not included in the pooled estimate.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- promssupp20261023.docx
- AIHA.xlsx
- PRISMA2020checklist.docx
- ITP.xlsx