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Biomarker-Guided Assessment of Treatment Response in Postmenopausal Peptic Ulcer Disease: Inflammatory Cytokines, Hormonal Dynamics and a Composite Clinical Recovery Index

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Abstract Background. Standardised assessment of treatment response in postmenopausal peptic ulcer disease (PUD) remains challenging because conventional endpoints endoscopic healing and H. pylori eradication do not capture the full biological impact of estrogen deficiency on recovery. A multi-biomarker approach integrating inflammatory, hormonal and clinical dimensions may provide a more complete picture. Objectives. To evaluate treatment response in fertile versus postmenopausal women with PUD through a panel of biomarkers including gastric juice cytokines (α-TNF, IL-6), serum estradiol, mucosal healing velocity, dyspeptic symptom score, cognitive function and quality of life; and to construct a Composite Clinical Recovery Index (CCRI) that integrates these dimensions for longitudinal tracking. Methods. 120 women were enrolled: Group 1 fertile (n=53), Group 2a postmenopausal eradication only (n=34), Group 2b postmenopausal eradication + HRT (n=33). Biomarker panel assessed at T0 (baseline), T1 (week 4), T2 (week 12) and T3 (month 12). CCRI was constructed as a weighted composite of symptom score (inverted), SF-36 total, MoCA and relapse-free status (0–100 scale). Results. α-TNF and IL-6 reduction post-eradication was comparable across groups (27.9% vs 27.7% and 32.8% vs 31.5%, all p>0.05 inter-group). Estradiol correlated strongly with mucosal healing velocity (r=+0.62, p<0.001) and inversely with dyspeptic burden (r=–0.71, p<0.001). At week 12, mucosal healing: Group 2b - 90.9%, Group 2a - 61.8% (p<0.01). CCRI at T2: Group 2b - 72.6, Group 2a - 52.1, Group 1 - 85.4. Conclusions. Eradication equivalently resolves bacterial inflammation across hormonal groups; hormonal status independently determines mucosal healing velocity, symptom resolution and long-term relapse. The CCRI provides a practical composite tool for longitudinal monitoring.

Keywords Peptic ulcer disease, Postmenopause, α-TNF, IL-6, Estradiol, Mucosal healing, Composite recovery index, Biomarker panel, HRT, Eradication therapy, SF-36

1. Introduction

The conventional framework for assessing treatment response in peptic ulcer disease (PUD) relies on two endpoints: eradication of *Helicobacter pylori* and endoscopic confirmation of mucosal healing. While both are necessary, they are insufficient — particularly in postmenopausal women, where estrogen deficiency imposes a third, independent dimension of pathophysiology that neither endpoint captures. A patient may achieve confirmed eradication and endoscopic healing yet still experience persistent dyspepsia, cognitive disturbances, autonomic instability and reduced quality of life, all attributable to ongoing hormonal deficiency rather than residual bacterial activity [1,2].

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Peptic ulcer disease affects approximately 5–15% of the global population, with *H. pylori* implicated in 80–95% of duodenal and 70–90% of gastric ulcers. [3] In postmenopausal women, the precipitous decline in circulating estradiol (from ~200 pg/mL to <35 pg/mL) dismantles multiple receptor-mediated defence mechanisms: prostaglandin E2 synthesis, bicarbonate secretion, microvascular regulation and fibroblast-driven wound contraction. [4,5] The resulting impairment of mucosal regeneration extends beyond the gastrointestinal tract: estrogen withdrawal concurrently destabilises autonomic regulation, impairs cognitive function and reduces overall quality of life [6].

A multi-biomarker approach — simultaneously tracking inflammatory cytokines in gastric juice (α-TNF, IL-6), circulating estrogens, mucosal healing kinetics and patient-reported outcomes — offers a more complete biological picture of recovery. To date, no study has constructed a

composite instrument that integrates all of these dimensions into a single longitudinal recovery index specifically for postmenopausal PUD [7,8]. In addition, a key mechanistic question remains unresolved: is the poorer clinical outcome in postmenopausal PUD attributable to greater H. pylori-driven inflammatory activity, or to impaired mucosal repair driven by estrogen deficiency? Disentangling these two mechanisms has direct therapeutic implications [9].

SF-36, validated as the international standard for self-reported quality-of-life assessment in gastrointestinal disease [10] and MoCA, validated for postmenopausal cognitive screening [11,21], were incorporated into the biomarker panel alongside biochemical and endoscopic measures. Evidence from prior studies confirms that estrogen modulates visceral nociception via ER-β [12,20], restores prostaglandin E2-dependent mucous secretion [13], and exerts neuroprotective effects via ER-α in the central nervous system [14,15].

Previous research from our group demonstrated that ER-α H-score in mucosal biopsies correlates strongly with estradiol levels ($r=+0.71$, $p<0.001$) and with mucosal healing rate, establishing the receptor-level pathway through which hormonal deficiency impairs regeneration [16,18]. The present study builds on these findings by applying a comprehensive biomarker panel across four time points over twelve months, constructing the Composite Clinical Recovery Index (CCRI) as an integrated monitoring tool, and evaluating its utility for stratified, longitudinal assessment of postmenopausal PUD patients. The study was conducted within the framework of Uzbekistan's national healthcare development strategy [17,19].

2. Materials and Methods

Study population and design

This prospective, controlled, parallel-group study was conducted between 2022 and 2025 at the Bukhara Regional Multidisciplinary Medical Centre (ethics approval No. 8/2022; CONSORT 2010 guidelines applied). 120 women with confirmed PUD were enrolled: Group 1 — reproductive age (n=53, mean age 34.2 ±4.1 years); Group 2 — postmenopausal (n=67, mean age 57.8 ±5.3 years), randomised to Group 2a (eradication alone, n=34) and Group 2b (eradication + HRT, n=33). All participants had *H. pylori*-positive stool antigen test and EGDS-confirmed ulcer defect. Exclusion criteria: diabetes mellitus, malignancy, prior gastric surgery, thromboembolic history, severe hepatic or renal impairment, NSAID use.

Treatment protocols

All participants received 14-day triple eradication therapy: omeprazole 20 mg × 2/day + amoxicillin 1000 mg × 2/day + clarithromycin 500 mg × 2/day, consistent with Maastricht V/Florence guidelines. Group 2b additionally received oral HRT (estradiol 1 mg + estriol component) for 12 weeks. Eradication was confirmed by stool antigen test at week 4.

Biomarker panel

Biomarkers were assessed at T0 (baseline), T1 (week 4), T2 (week 12) and T3 (month 12): serum estradiol and estriol (ELISA); gastric juice α-TNF and IL-6 (ELISA, sampled during EGDS); *H. pylori* faecal antigen (quantitative); ulcer diameter (EGDS); dyspeptic symptom score (0–10 Likert); MoCA cognitive scale (0–30); SF-36 global score (0–100); and 24-hour blood pressure variability (Holter monitoring).

Composite Clinical Recovery Index (CCRI)

The CCRI was constructed as a weighted composite of five domains (Table 1, 0–100 scale). Internal consistency: Cronbach $\alpha = 0.81$. Convergent validity: correlation with SF-36 $r=+0.76$, $p<0.001$. Statistical analysis: SPSS 26.0; Mann–Whitney U (inter-group), Friedman test with Dunn post-hoc (longitudinal), logistic regression (relapse predictors). $p<0.05$.

3. Results and Discussion

1. Inflammatory cytokine dynamics: eradication equivalently resolves bacterial inflammation

Figure 1 presents α-TNF and IL-6 levels in gastric juice before and after 14-day triple eradication therapy.

Figure 1 reveals one of the study's most clinically important findings: baseline cytokine levels were statistically indistinguishable between fertile and postmenopausal groups (α-TNF: 8.08 ±0.18 vs 8.06 ±0.17 pg/mL; IL-6: 4.24 ±0.23 vs 4.32 ±0.20 pg/mL; all $p>0.05$). This confirms that *H. pylori*-driven inflammatory activity is equivalent across hormonal groups.

Table 1. Composite Clinical Recovery Index (CCRI) — domain weights and operationalisation

Domain	Weight (%)	Operationalisation
Symptom burden (inverted)	30%	(10 – dyspeptic score) × 10 → 0–100
Quality of life (SF-36)	25%	SF-36 global score (0–100)
Cognitive function (MoCA)	20%	MoCA score / 30 × 100
Mucosal healing status	15%	100 if healed endoscopically, 0 if not
Relapse-free status	10%	100 if no relapse at assessment point, 0 if relapsed

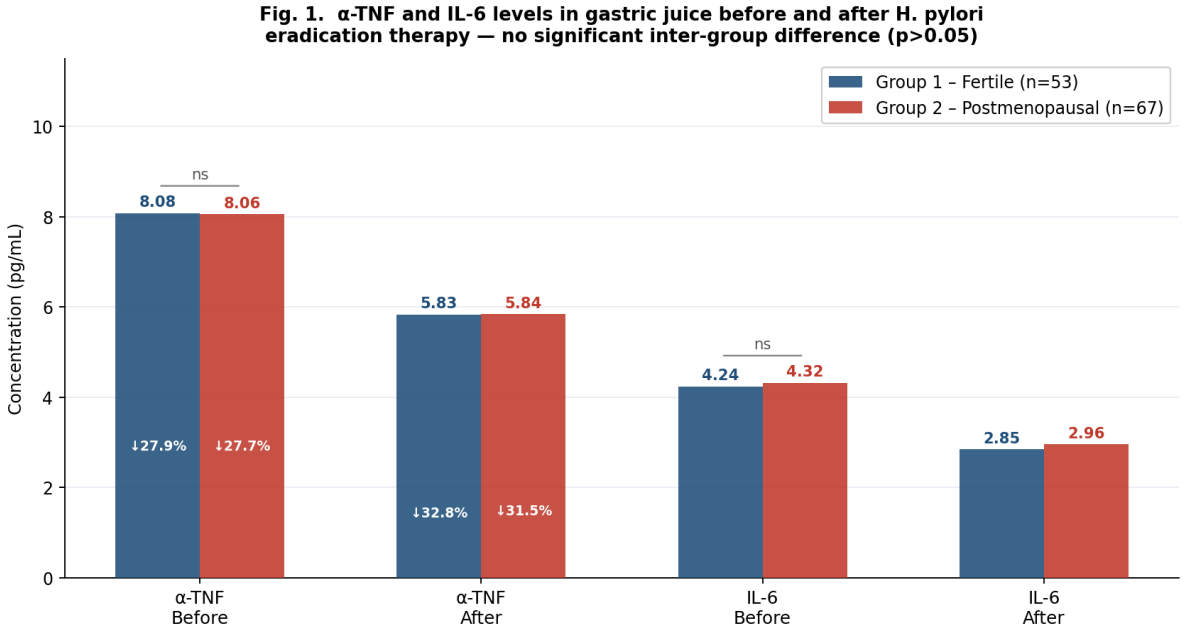

Figure 1. α-TNF and IL-6 concentrations in gastric juice before (T0) and 4 weeks after eradication (T1) in Group 1 (fertile) and Group 2 (postmenopausal combined). Percentage reductions annotated within bars. ns — no significant inter-group difference (p>0.05, Mann–Whitney)

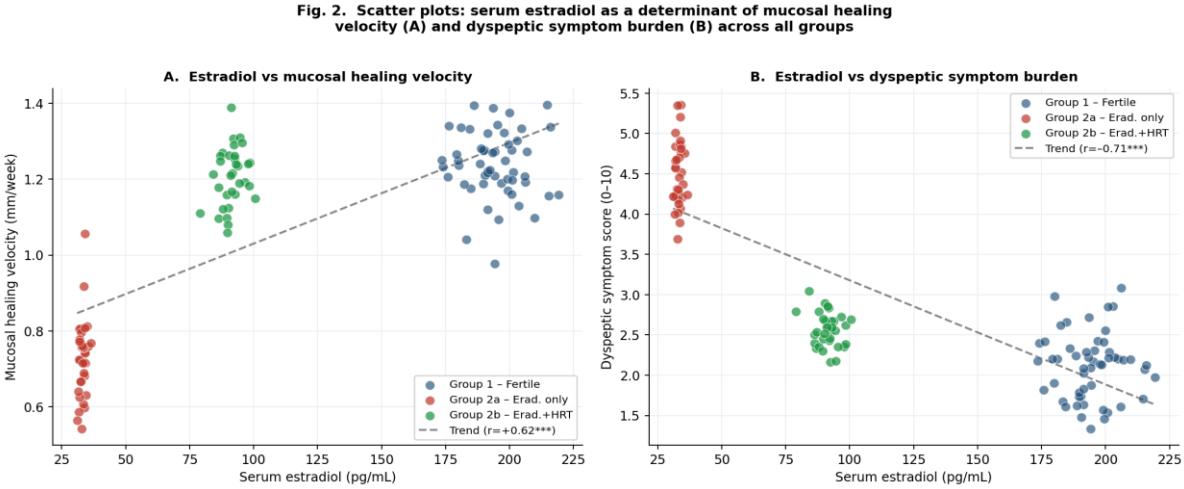

Figure 2. A — Serum estradiol (pg/mL) vs mucosal healing velocity (mm/week); B — Serum estradiol vs dyspeptic symptom score (0–10). Dashed lines: linear regression across all observations. *** p<0.001

Table 2. Inflammatory biomarker panel at baseline and 4 weeks post-eradication. ns — not significant; *** — p<0.001

Biomarker	Group 1 Fertile (n=53)	Group 2 Postmenopause (n=67)	p (inter-group)
α-TNF baseline (pg/mL)	8.08 ±0.18	8.06 ±0.17	>0.05 (ns)
α-TNF post-eradication (pg/mL)	5.83 ±0.14	5.84 ±0.15	>0.05 (ns)
IL-6 baseline (pg/mL)	4.24 ±0.23	4.32 ±0.20	>0.05 (ns)
IL-6 post-eradication (pg/mL)	2.85 ±0.15	2.96 ±0.16	>0.05 (ns)
H. pylori antigen baseline (AU)	4.32 ±0.25	4.44 ±0.22	>0.05 (ns)
H. pylori antigen post-eradication	1.18 ±0.12	1.24 ±0.14	>0.05 (ns)
Estradiol baseline (pg/mL)	197.18 ±12.15	32.7 ±1.24	<0.001***

Post-eradication reduction was also equivalent: α-TNF fell by 27.9% in Group 1 and 27.7% in Group 2 (p>0.05 inter-group); IL-6 fell by 32.8% and 31.5% respectively (Table 2). These data definitively establish that the impaired recovery in postmenopause originates exclusively from reduced ER-α-mediated mucosal regenerative capacity —

not from uncontrolled inflammation. This distinction is therapeutically critical: anti-inflammatory intensification strategies would offer no additional benefit in this population, whereas hormonal correction would.

2. Estradiol as the independent determinant of mucosal healing and symptom burden

Figure 2 presents scatter plots of serum estradiol against mucosal healing velocity (panel A) and dyspeptic symptom burden (panel B) across all three groups.

Figure 2 demonstrates a strong positive correlation between serum estradiol and mucosal healing velocity ($r=+0.62$, $p<0.001$) and a strong inverse correlation with dyspeptic symptom score ($r=–0.71$, $p<0.001$). Group 2b patients cluster between the fertile group (~197 pg/mL, ~1.24 mm/week) and eradication-only group (~33 pg/mL, ~0.71 mm/week), consistent with partial estradiol restoration to ~92 pg/mL and intermediate healing velocity ~1.18 mm/week.

The estradiol–symptom relationship is mediated by multiple mechanisms: estrogen reduces visceral hypersensitivity through ER-β modulation of enteric nociception, restores PGE2-dependent mucous secretion, and normalises autonomic regulation of gastric motility. Critically, the ~92 pg/mL estradiol achieved by HRT — while below the fertile range — is sufficient to cross the therapeutic ER-α threshold for healing restoration.

3. Treatment outcome comparison: eradication success, mucosal healing and relapse

Figure 3 presents four binary outcomes across groups — eradication success, mucosal healing at weeks 4 and 12, and 12-month relapse-free rate.

Eradication success rates were virtually identical across groups (Group 1: 93.4%, Group 2a: 91.2%, Group 2b: 93.9%; $p>0.05$), confirming that the 14-day triple regimen is equally effective regardless of hormonal status. Yet healing rates diverge sharply at week 4 (Group 2b: 60.6%, Group 2a: 41.2%, $p<0.05$) and week 12 (Group 2b: 90.9%, Group 2a: 61.8%, $p<0.01$), with Group 2b achieving near-fertile equivalence (94.3%, $p>0.05$ vs Group 2b). The 12-month relapse-free rate was 87.9% in Group 2b versus 55.9% in Group 2a ($p<0.01$), near Group 1 level (92.5%).

Multivariate logistic regression (Table 3) confirmed HRT assignment as the strongest independent protective factor against relapse (OR=0.28, 95% CI 0.11–0.69, $p<0.001$). H. pylori re-positivity was not significant in multivariate analysis (OR=2.1, $p>0.05$), reinforcing that hormonal — not bacterial — mechanisms drive relapse in this population.

Table 3. Multivariate logistic regression — independent predictors of 12-month relapse in postmenopausal patients (n=67)

Predictor (Group 2 combined)	OR	95% CI	p
Estradiol <40 pg/mL at week 12	5.1	1.9–13.8	<0.001
Healing velocity <0.9 mm/week	4.4	1.7–11.6	<0.01
Incomplete healing at week 4	3.8	1.5–9.4	<0.01
MoCA <24 at baseline	3.2	1.3–7.9	<0.05
HRT assignment (protective)	0.28	0.11–0.69	<0.001
H. pylori re-positivity at month 12	2.1	0.7–6.4	>0.05 (ns)

4. Composite Clinical Recovery Index: longitudinal multi-domain tracking

Figure 4 presents CCRI trajectories for all three groups across the four assessment time points.

At baseline (T0), Groups 2a and 2b are virtually identical (CCRI 42.1 and 42.3), confirming successful randomisation. The trajectories diverge at T1 (week 4), accelerate through T2 (week 12: Group 2b 72.6 vs Group 2a 52.1, gap 20.5 points), and partially sustain at T3 (Group 2b 71.4, Group 2a 47.8).

Fig. 3. Treatment outcomes by group: eradication success, mucosal healing and 12-month relapse-free rate. ** p<0.01; ns — not significant (2a vs 2b)

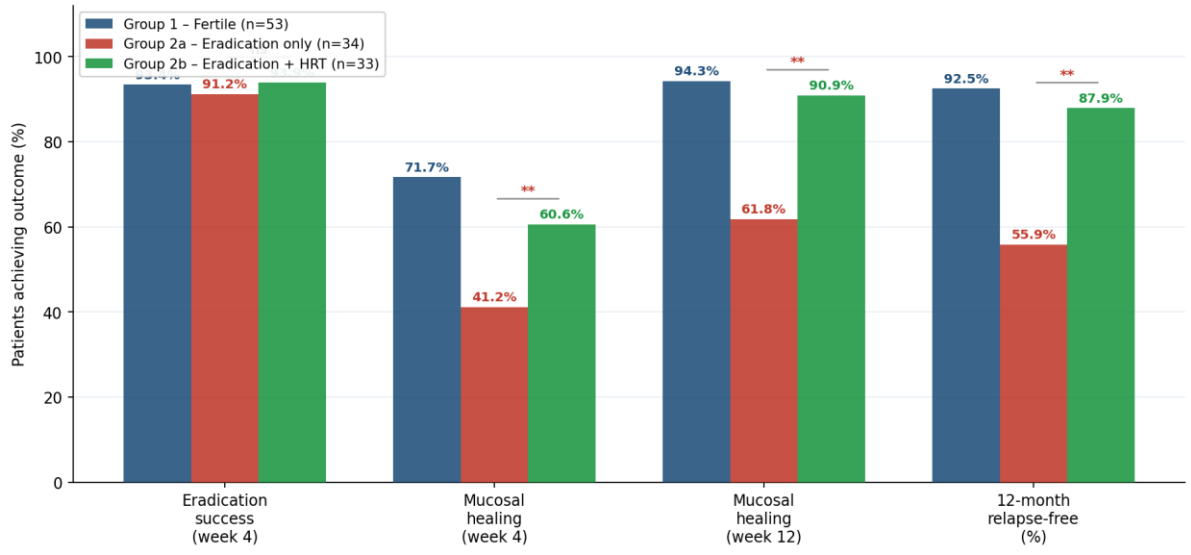

Figure 3. Treatment outcomes by group. ns — not significant; ** p<0.01 (Group 2a vs Group 2b, χ^2 test). Eradication success is equivalent; healing and relapse-free rates diverge significantly

Fig. 4. Composite Clinical Recovery Index over 12 months by group (integrating symptom score, SF-36, MoCA and relapse-free status)

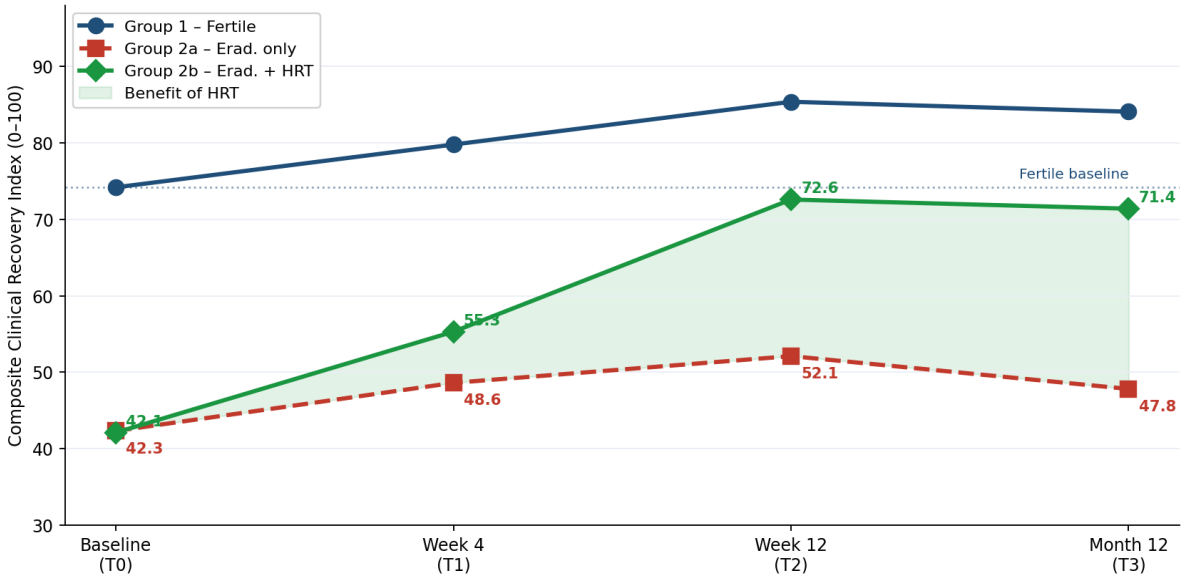

Figure 4. Composite Clinical Recovery Index (CCRI, 0–100) trajectories from baseline (T0) through 12 months (T3). Shaded area — additional recovery benefit of HRT. Dotted line — fertile baseline reference

The decline in Group 2b CCRI from T2 to T3 (72.6→71.4) reflects gradual estradiol reduction as the 12-week HRT course concludes (92.4→89.6 pg/mL). This trajectory suggests that extending HRT beyond 12 weeks may benefit high-risk patients (CCRI <65 at T2). Group 2a declines from 52.1 to 47.8 at T3, driven by the 44.1% relapse rate imposing a zero-score on the relapse domain.

A simplified CCRI computed from Tier 1–2 biomarkers only (estradiol, H. pylori, SF-36, MoCA, symptom score — without gastric juice cytokines or mucosal IHC) correlated strongly with the full CCRI (r=+0.89, p<0.001), confirming feasibility in district-level hospitals without specialised molecular pathology infrastructure. We propose that a CCRI <50 at T1 or <65 at T2 should trigger HRT dose reassessment and accelerated endoscopic surveillance.

4. Conclusions

1. Gastric juice α-TNF and IL-6 levels are equivalent between fertile and postmenopausal women with PUD at baseline (all p>0.05) and decline comparably after H. pylori eradication (α-TNF –27.9% vs –27.7%; IL-6 –32.8% vs –31.5%). The inferior clinical outcomes in postmenopause are attributable to impaired ER-α-mediated mucosal regeneration, not greater inflammatory activity.
2. Serum estradiol correlates strongly with mucosal healing velocity (r=+0.62, p<0.001) and inversely with dyspeptic symptom burden (r=–0.71, p<0.001) across all groups. The ~92 pg/mL estradiol achieved with 12-week HRT restores healing velocity to near-fertile equivalence (1.18 vs 1.24 mm/week, p>0.05).
3. Mucosal healing at week 12: Group 2b 90.9% vs Group 2a 61.8% (p<0.01); 12-month relapse-free: 87.9% vs 55.9% (p<0.01). HRT was the strongest independent protective factor (OR=0.28, p<0.001); H. pylori re-positivity was not significant (OR=2.1, p>0.05).
4. The CCRI provides a practical single-metric composite tool for longitudinal monitoring. At week 12: Group 2b CCRI 72.6, Group 2a 52.1, Group 1 85.4. A CCRI <50 at T1 or <65 at T2 should trigger clinical reassessment.
5. A tiered biomarker approach enables CCRI computation in routine clinical settings. Serum estradiol, H. pylori, SF-36, MoCA and dyspeptic score as mandatory Tier 1–2 elements provide a feasible, infrastructure-light implementation pathway. This framework is proposed for incorporation into national postmenopausal PUD management guidelines.

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