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Sex-Stratified Analysis of Maximum Squeeze Pressure Interaction with Rectal Push Pressure and Rectoanal Inhibitory Reflex in External Rectal Prolapse Using High-Resolution Anorectal Manometry

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Abstract

Purpose External rectal prolapse (ERP) carries high risks of recurrence, incontinence, and constipation. Which three-dimensional high-resolution anorectal manometry (3D HR-ARM) phenotype identifies the most severe functional impairment remains undefined. We established a sex-stratified interaction model between maximum squeeze pressure (MSP) and rectal push pressure (RPP) or the rectoanal inhibitory reflex (RAIR).

Methods In this retrospective case–control study, 167 patients with ERP (69 women, 98 men) and 142 healthy volunteers (HVs) underwent 3D HR-ARM, and defecography was performed in all ERP patients. Logistic regression and Rothman's additive interaction models quantified MSP–RPP (women) and MSP–RAIR (men) interactions, with bootstrap 95% confidence intervals (CIs).

Results In women, the R_{11} phenotype (concomitant MSP and RPP reduction) carried the highest odds of ERP (odds ratio [OR] 213.50, 95% CI 52.50–773.56), with a super-additive effect (S = 6.14). In men, reduced MSP with preserved RAIR (R_{10}) carried the highest odds (OR 21.50, 95% CI 6.43–119.07), and the MSP–RAIR interaction was antagonistic (S = 0.31; multiplicative interaction OR 0.12, P = 0.025). R_{11} specificity was 98.6% in women and 88.6% in men. Combined MSP + RPP and MSP + RAIR models yielded areas under the curve of 0.938 and 0.731.

Conclusions Sex-specific interaction phenotyping of 3D HR-ARM reveals divergent pathophysiological patterns in ERP—synergistic MSP–RPP failure in women and MSP-dominant dysfunction with antagonistic RAIR modulation in men—and, integrated with defecography-based anatomical classification, may inform risk stratification and individualized surgical planning.

Introduction

External rectal prolapse (ERP) is a pathological condition characterized by full-thickness protrusion of the rectal wall outside the anus. Globally, the incidence of ERP in adults ranges from 0.25% to 0.4%, with a significantly higher prevalence in women than in men (approximately 6:1), particularly among multiparous women [1, 2]. Male patients commonly present with chronic constipation, a history of prostate surgery, or neurological diseases [3]. Typical manifestations include anal mass protrusion accompanied by mucus exudation or bleeding; in severe cases, strangulation necrosis may occur [4].

ERP pathogenesis involves a unique tripartite interaction among neural, muscular, and structural factors. Rectal wall prolapse causes mechanical damage to the anal sphincter. Simultaneously, the absence of the rectoanal inhibitory reflex (RAIR) and changes in rectal compliance form a vicious cycle [5–7]. While the diagnosis of ERP is established clinically by physical examination, preoperative evaluation relies on two complementary modalities: (i) X-ray defecography for structural assessment and (ii) three-dimensional high-resolution anorectal manometry (3D HR-ARM) for functional assessment [8]. Through pressure contour maps, 3D HR-ARM can precisely locate high- or low-pressure areas of sphincter dysfunction that are unattainable using traditional imaging methods [9, 10].

However, current research faces three major challenges in functional assessment and risk stratification: (i) isolation of parameters leads to a 30% false-positive rate in healthy individuals [11]; (ii) the complexity of principal component analysis models hinders clinical translation [11, 12]; and (iii) the lack of prognostic prediction results in a 15% postoperative complication rate [13] and 5-year recurrence rates as high as 30% [14].

In this study, we adopted a multi-parameter interaction analysis strategy. Using sex stratification and threshold adjustment principles proposed by Jutras et al. [15], we evaluated the ability of interactions between maximum squeeze pressure (MSP) and either rectal push pressure (RPP) or rectoanal inhibitory reflex (RAIR) to discriminate patients with ERP from healthy volunteers (HVs). Our objective was to define an easily recognizable high-risk functional phenotype by integrating 3D HR-ARM interaction metrics with defecographic classification, thereby providing an evidence-based basis for preoperative risk stratification and individualized treatment planning.

Methods

Study design and participants

This retrospective observational case–control study enrolled 167 patients (69 women and 98 men) diagnosed with ERP who underwent surgical treatment at Tianjin Union Medical Center between January 2020 and March 2026. All patients underwent X-ray barium defecography and 3D HR-ARM. A control group of 142 healthy volunteers (72 women and 70 men) underwent 3D HR-ARM after comprehensive anorectal functional assessment during the same period. The two groups differed significantly in age within each sex (ERP patients were younger; see Results). This study adhered to the STROBE guidelines for observational research [16] and was approved by the Institutional Ethics Committee (2024B134). Written informed consent was obtained from all healthy volunteers; for ERP patients, the requirement for individual consent was waived by the Ethics Committee. The study complied with the Declaration of Helsinki [17].

Inclusion and exclusion criteria

HVs: (i) age 18–85 years; (ii) no evidence of systemic disease (cardiovascular, respiratory, or gastrointestinal) or functional bowel disorders (assessed by interview and Wexner constipation score < 5, per the Rome IV framework [18]); (iii) normal digital rectal examination; (iv) no laxative use in the preceding 3 months; and (v) no history of anorectal surgery or trauma.

ERP patients: (i) age 18–85 years; (ii) full-thickness rectal wall protrusion extending visibly beyond the anal verge at rest or on straining (Oxford rectal prolapse grade V [19]), confirmed by objective clinical examination; (iii) symptomatic ERP (fecal incontinence, constipation, incomplete evacuation, pain, rectal bleeding, mucus discharge, or quality-of-life impairment); and (iv) defecography-confirmed ERP with concomitant abnormalities (rectocele, pelvic floor hernia/internal rectal intussusception, sacrum–rectal

separation, megarectum, or puborectalis hypertrophy). Exclusion criteria: (i) pregnancy; (ii) chronic systemic disease (cardiac, pulmonary, hepatic, or renal insufficiency); (iii) history of surgery for pelvic organ prolapse; (iv) third- or fourth-degree obstetric trauma; and (v) mental disorders or poor compliance.

3D HR-ARM protocol

Procedures followed the guidelines of the International Anorectal Physiology Working Group [20]. After administration of an 80-mL glycerin enema, a ManoScan 3D probe (Sierra Scientific Instruments, Los Angeles, CA, USA) was inserted 10 cm into the rectum. Probe specifications: (i) diameter 10 mm, sensitive length 64 mm; (ii) 256 circumferential sensors (axial spacing 4 mm; circumferential spacing 2 mm); and (iii) calibration range 0–300 mmHg.

Procedure details: (i) preparation—digital rectal examination to assess for residual stool; (ii) positioning—left lateral decubitus with flexed hips and knees, probe orientation confirmed via handle alignment; (iii) data acquisition—resting pressure (60-s recording), short (5 s) and sustained (20–30 s) squeezes (best of three short squeezes analyzed), a single forceful cough (two trials), simulated defecation (three 15-s attempts to expel the probe), RAIR elicitation (balloon distension in 10–50 mL increments), and sensory testing (stepwise inflation of 10–300 mL to determine first sensation, urge, and maximum tolerated volume). Pressure measurements were referenced to atmospheric pressure.

Phenotypic classification (study-derived thresholds; dichotomized as R_0 = normal, R_1 = reduced): women—MSP: $R_0 \geq 114$ mmHg, $R_1 < 114$ mmHg; RPP: $R_0 \geq 26$ mmHg, $R_1 < 26$ mmHg; men—MSP: $R_0 \geq 150$ mmHg, $R_1 < 150$ mmHg; RAIR: $R_0 > 10$ mL, $R_1 \leq 10$ mL. R_{00} denotes both parameters normal, R_{11} both reduced, R_{10} reduced MSP only, and R_{01} reduced RPP (women) or RAIR (men) only. Phenotype thresholds were derived from the ROC-optimal cut-offs in the present cohort, rounded to clinically convenient integer values (female MSP 113.2 → 114 mmHg; male MSP 150.0 → 150 mmHg); for RAIR, the phenotype threshold (≤ 10 mL) denotes an impaired reflex, whereas ROC analysis independently identified complete absence of the reflex (0 mL) as the most specific discriminator. All ROC analyses were performed on the original continuous measurements.

Statistical analysis

Statistical analyses were performed using SPSS 22.0 (IBM, Chicago, IL, USA) and R (version 4.3.2). Normality of continuous variables was assessed using the Shapiro–Wilk test. Continuous variables are presented as mean ± SD and compared using the independent-samples t-test (Welch's correction where variances were unequal, assessed by Levene's test). Categorical variables are reported as n (%) and compared using the chi-square test. Associations between phenotypes and ERP were estimated using logistic regression with the R_{00} phenotype as the reference, reported as odds ratios (ORs) with 95% confidence intervals (CIs). Additive interaction was quantified using Rothman's measures [21]: the relative excess risk due to interaction (RERI) = $R_{11} - R_{10} - R_{01} + 1$, the attributable proportion due to

interaction (AP) = RERI/R_{11}, and the synergy index (S) = (R_{11} − 1)/[(R_{10} − 1) + (R_{01} − 1)], where R denotes the OR of each phenotype relative to R_{00}. These measures were calculated from the phenotype-specific ORs (Table 3), which derive from the cross-tabulated counts in Tables 4 and 5; e.g., in women, RERI = 213.50 (R_{11}) − 12.20 (R_{10}) − 24.40 (R_{01}) + 1 = 177.90, and in men, RERI = 7.93 − 21.50 − 3.01 + 1 = − 15.58. 95% CIs were obtained by bootstrap resampling (20,000 iterations, stratified by case–control status). Multiplicative interaction was assessed by including a product term (MSP × RPP in women; MSP × RAIR in men) in the logistic model; the exponentiated coefficient of this term equals $R_{11}/(R_{01} \times R_{10})$, i.e., the joint OR divided by the product of the two single-phenotype ORs, and a value departing from 1 indicates interaction on the multiplicative scale. Two-tailed $P < 0.05$ was considered statistically significant. As a sensitivity analysis for the age imbalance between groups, manometric parameters were compared between ERP patients aged ≥ 50 years and < 50 years within each sex, and case–control comparisons were repeated within the ≥ 50-year stratum, using Welch's t-test with Bonferroni correction for multiple comparisons (Supplementary Tables S1 and S2). Rectal compliance was excluded a priori because technically reliable compliance values could not be derived from the archived recordings in either sex.

Table 3
Phenotype-stratified odds ratios (95% CI) for ERP by logistic regression, with R_{00} as the reference

Phenotype	**Female ERP/HVs, n**	**OR (95% CI)**	**Male ERP/HVs, n**	**OR (95% CI)**
R_{00} (both normal) — reference	10/61	1.00	21/43	1.00
R_{01} (reduced RPP or RAIR only)	8/2	24.40 (5.73–161.00)	25/17	3.01 (1.36–7.30)
R_{10} (reduced MSP only)	16/8	12.20 (4.45–46.08)	21/2	21.50 (6.43–119.07)
R_{11} (both reduced)	35/1	213.50 (52.50–773.56)	31/8	7.93 (3.40–25.41)

MSP, maximum squeezing pressure; RPP, rectal push pressure; RAIR, rectoanal inhibitory reflex.

Table 4
Cross-tabulation of MSP and RPP phenotypes among female ERP patients and healthy female volunteers

MSP	ERP (n = 69)	HVs (n = 72)	Total	ERP (n = 69)	HVs (n = 72)	Total
	RPP ≥ 26 mmHg (R_0)			RPP < 26 mmHg (R_1)		
MSP ≥ 114 mmHg (R_0)	10	61	71	8	2	10
MSP < 114 mmHg (R_1)	16	8	24	35	1	36
Total	26	69	95	43	3	46

Phenotypes: R_{00} = both normal; R_{01} = reduced RPP only; R_{10} = reduced MSP only; R_{11} = both reduced.
MSP, maximum squeezing pressure; RPP, rectal push pressure; ERP, external rectal prolapse; HVs, healthy volunteers.

Table 5
Cross-tabulation of MSP and RAIR phenotypes among male ERP patients and healthy male volunteers

RAIR	ERP (n = 98)	HVs (n = 70)	Total	ERP (n = 98)	HVs (n = 70)	Total
	MSP ≥ 150 mmHg (R_0)			MSP < 150 mmHg (R_1)		
RAIR > 10 mL (R_0)	21	43	64	21	2	23
RAIR ≤ 10 mL (R_1)	25	17	42	31	8	39
Total	46	60	106	52	10	62

Phenotypes: R_{00} = both normal; R_{01} = reduced RAIR only; R_{10} = reduced MSP only; R_{11} = both reduced.

Results

Participant characteristics

A total of 309 participants were enrolled: 167 (69 women, 98 men) and 142 (72 women, 70 men) in the ERP and HV groups, respectively. Female ERP patients were younger than female HVs (58.61 ± 14.18 vs. 64.71 ± 8.53 years, Welch $P = 0.003$) and had a higher BMI (24.13 ± 2.31 vs. 20.34 ± 1.18 kg/m², $P < 0.001$); male ERP patients were substantially younger than male HVs (40.04 ± 18.19 vs. 64.60 ± 9.47 years, $P < 0.001$) and also had a higher BMI (25.39 ± 1.79 vs. 22.67 ± 0.64 kg/m², $P < 0.001$). Age-adjusted Firth penalized logistic regression was therefore additionally performed for the key phenotype associations (female R_{11}: adjusted OR 144.97, 95% CI 23.78–883.72; male R_{10}: adjusted OR 16.96, 95% CI 3.04–94.49; both remained the highest-odds phenotypes in their sex strata). No manometric

parameter differed significantly between ERP patients aged ≥ 50 and < 50 years in either sex after Bonferroni correction, and the case–control differences in the principal pressure parameters persisted within the ≥ 50-year stratum (Supplementary Tables S1 and S2), indicating that the manometric phenotypes were not driven by age.

Univariate and multivariate analyses

Female ERP patients showed significantly lower maximum and mean resting pressure, high-pressure zone (HPZ) length, MSP, RPP, and residual anal pressure, along with a higher anal relaxation rate and a less negative rectoanal pressure gradient compared with female HVs (all $P < 0.01$); RAIR and rectal sensory thresholds did not differ significantly (Table 1). Male ERP patients showed significantly lower maximum and mean resting pressure, HPZ length, MSP, residual anal pressure, anal relaxation rate, and RAIR threshold (all $P < 0.01$), together with a less negative rectoanal pressure gradient ($P < 0.01$); rectal push pressure did not differ between groups ($P = 0.20$), whereas the urge-to-defecate threshold and maximum tolerated volume were higher in male ERP patients ($P = 0.01$ and $P = 0.05$, respectively) (Table 1).

Table 1
Comparison of 3D HR-ARM parameters between healthy volunteers (HVs) and ERP patients, stratified by sex

Variable	Female HVs (n = 72)	Female ERP (n = 69)	Mean difference (95% CI)	*P*	Male HVs (n = 70)	Male ERP (n = 98)	Mean difference (95% CI)	*P*
Rest								
Maximum resting pressure (mmHg)	77.61 ± 15.94	47.47 ± 28.46	30.14 (22.39 to 37.89)	< 0.01	81.23 ± 15.50	58.14 ± 26.99	23.09 (16.58 to 29.60)	< 0.01
Mean resting pressure (mmHg)	70.58 ± 14.67	41.45 ± 24.37	29.13 (22.38 to 35.88)	< 0.01	71.83 ± 14.82	51.65 ± 24.39	20.18 (14.19 to 26.17)	< 0.01
HPZ length (cm)	3.73 ± 0.61	3.25 ± 1.11	0.48 (0.18 to 0.78)	< 0.01	4.08 ± 0.73	3.34 ± 0.77	0.74 (0.51 to 0.97)	< 0.01
Squeeze								
Maximum squeezing pressure (mmHg)	168.03 ± 47.01	91.62 ± 47.86	76.41 (60.61 to 92.21)	< 0.01	215.17 ± 71.20	158.09 ± 81.52	57.08 (33.69 to 80.47)	< 0.01
Duration of sustained squeeze (s)	14.92 ± 5.93	99.02 ± 45.94	-84.10 (-95.22 to -72.98)	< 0.01	14.31 ± 5.94	13.70 ± 6.38	0.61 (-1.28 to 2.50)	0.53
Simulated defecation								
Residual anal pressure (mmHg)	71.77 ± 25.51	14.02 ± 6.02	57.75 (51.59 to 63.91)	< 0.01	88.86 ± 24.50	73.84 ± 29.58	15.02 (6.76 to 23.28)	< 0.01
Anal relaxation rate (%)	23.07 ± 18.63	58.94 ± 29.81	-35.87 (-44.20 to -27.54)	< 0.01	20.04 ± 19.85	9.56 ± 17.36	10.48 (4.65 to 16.31)	< 0.01
Rectal push pressure (mmHg)	44.62 ± 17.36	10.74 ± 32.43	33.88 (25.14 to 42.62)	< 0.01	50.07 ± 23.96	55.03 ± 25.62	-4.96 (-12.59 to 2.67)	0.20

Values are mean ± SD. Mean differences (HVs − ERP) with 95% CIs and P values were calculated using Welch's t-test. HPZ, high-pressure zone. Note: In female ERP patients, the recorded duration of sustained squeeze (99.02 ± 45.94 s; range 10.9–257.9 s) far exceeded the instructed 20–30-s maneuver. Because a maximal voluntary contraction cannot be maintained for this duration, these recordings are likely to reflect prolonged paradoxical contractions rather than true sustained squeezes; this should be considered when interpreting this parameter.

Variable	Female HVs (n = 72)	Female ERP (n = 69)	Mean difference (95% CI)	*P*	Male HVs (n = 70)	Male ERP (n = 98)	Mean difference (95% CI)	*P*
Rectoanal pressure gradient (mmHg)	-27.14 ± 25.77	-6.13 ± 28.19	-21.01 (-30.02 to -12.00)	< 0.01	-37.81 ± 27.49	-18.91 ± 26.35	-18.90 (-27.26 to -10.54)	< 0.01
Graded balloon distension								
Rectoanal inhibitory reflex (mL)	17.64 ± 8.47	15.65 ± 13.11	1.99 (-1.71 to 5.69)	0.29	19.42 ± 8.99	13.78 ± 13.12	5.64 (2.27 to 9.01)	< 0.01
First sensation (mL)	40.97 ± 18.09	39.86 ± 26.43	1.11 (-6.47 to 8.69)	0.77	44.14 ± 27.21	45.41 ± 31.27	-1.27 (-10.22 to 7.68)	0.78
Urge to defecate (mL)	77.78 ± 34.73	78.26 ± 44.15	-0.48 (-13.75 to 12.79)	0.94	78.57 ± 33.72	93.77 ± 44.59	-15.20 (-27.13 to -3.27)	0.01
Maximum tolerated volume (mL)	132.08 ± 39.93	135.22 ± 43.78	-3.14 (-17.11 to 10.83)	0.66	133.43 ± 45.65	147.04 ± 41.77	-13.61 (-27.25 to 0.03)	0.05

Values are mean ± SD. Mean differences (HVs − ERP) with 95% CIs and P values were calculated using Welch's t-test. HPZ, high-pressure zone. Note: In female ERP patients, the recorded duration of sustained squeeze (99.02 ± 45.94 s; range 10.9–257.9 s) far exceeded the instructed 20–30-s maneuver. Because a maximal voluntary contraction cannot be maintained for this duration, these recordings are likely to reflect prolonged paradoxical contractions rather than true sustained squeezes; this should be considered when interpreting this parameter.

Sex-stratified Firth penalized logistic regression (Table 2) showed that, in women, lower MSP (OR per 10 mmHg 0.274, 95% CI 0.110–0.687, $P = 0.006$) and longer duration of sustained squeeze (OR per 10 s 3.313, 95% CI 1.532–7.162, $P = 0.002$) were associated with ERP, whereas RPP was not ($P = 0.249$). In men, lower MSP (OR per 10 mmHg 0.915, 95% CI 0.871–0.960, $P < 0.001$), shorter HPZ length (OR per cm 0.250, 95% CI 0.141–0.445, $P < 0.001$), and lower RAIR threshold volume (OR per 10 mL 0.713, 95% CI 0.518–0.982, $P = 0.038$) were associated with ERP; the RAIR association was attenuated and non-significant after age adjustment ($P = 0.295$).

Table 2
Sex-stratified Firth penalized logistic regression of 3D HR-ARM parameters associated with ERP

Variable	OR (95% CI)	*P*
Female		
Maximum squeezing pressure (per 10 mmHg)	0.274 (0.110–0.687)	0.006
Duration of sustained squeeze (per 10 s)	3.313 (1.532–7.162)	0.002
Rectal push pressure (per 10 mmHg)	1.235 (0.863–1.768)	0.249
Male		
Maximum squeezing pressure (per 10 mmHg)	0.915 (0.871–0.960)	< 0.001
HPZ length (per cm)	0.250 (0.141–0.445)	< 0.001
Rectoanal inhibitory reflex (per 10 mL)	0.713 (0.518–0.982)	0.038

Qualitative interaction analysis of MSP and RPP (women)

Using R_{00} as the reference, the odds of ERP were 24.40 (95% CI 5.73–161.00) for R_{01}, 12.20 (95% CI 4.45–46.08) for R_{10}, and 213.50 (95% CI 52.50–773.56) for R_{11} (Table 3), making R_{11} the highest-risk phenotype in women. In women, four phenotypes were defined by MSP and RPP status (Table 4; Fig. 1a): R_{00} (both normal), R_{10} (reduced MSP only), R_{01} (reduced RPP only), and R_{11} (both reduced). Because ($R_{11} - R_{00}$) far exceeded ($R_{10} - R_{00}$) + ($R_{01} - R_{00}$), the additive interaction between MSP and RPP reduction was positive (synergistic): concomitant reduction of the two parameters conferred substantially higher odds of ERP than expected from their individual effects. The R_{11} phenotype was present in 50.7% of female ERP patients (35/69) but only 1.4% of female healthy volunteers (1/72), corresponding to a specificity of 98.6% as a rule-in marker.

Qualitative interaction analysis of MSP and RAIR (men)

In men, the four phenotypes were defined by MSP status and RAIR threshold volume (R_{11} denoting reduced MSP with RAIR ≤ 10 mL; Table 5; Fig. 1b). Using R_{00} as the reference, the odds of ERP were 3.01 (95% CI 1.36–7.30) for R_{01} (RAIR impairment alone), 21.50 (95% CI 6.43–119.07) for R_{10} (reduced MSP alone), and 7.93 (95% CI 3.40–25.41) for R_{11} (Table 3). The qualitative pattern differed markedly from that in women: because ($R_{11} - R_{00}$) was smaller than ($R_{10} - R_{00}$) + ($R_{01} - R_{00}$), the additive interaction was negative (antagonistic)—in men with reduced MSP, the additional presence of RAIR impairment did not further increase the odds of ERP—and reduced MSP with preserved RAIR (R_{10}) was the highest-risk phenotype. The R_{11} phenotype was present in 31.6% of male ERP patients (31/98) versus 11.4% of male healthy volunteers (8/70), corresponding to a specificity of 88.6%.

Quantitative interaction analysis

In women, quantitative measures confirmed a strong positive additive interaction (Table 6): the synergy index *S* was 6.14 (95% CI 0.86–23.85), the relative excess risk due to interaction (RERI) was 177.90 (bootstrap 95% CI − 12.58 to 678.23), and the attributable proportion due to interaction (AP) was 83.3% (95% CI − 15.9% to 95.6%)—that is, among women with the R_{11} phenotype, an estimated 83% of the ERP odds were attributable to the interaction itself. The additive-scale confidence intervals did not exclude the null, reflecting the small numbers in certain phenotypic cells (e.g., one female control in the R_{11} phenotype); these estimates indicate uncertainty in the magnitude rather than the direction of the interaction and should be considered exploratory. No multiplicative interaction was detected (interaction OR 0.72, $P = 0.81$). Given the case–control design, prevalence-ratio-scale sensitivity analyses were not applicable and are not reported.

Table 6
Additive and multiplicative interaction measures for MSP–RPP (women) and MSP–RAIR (men).

Measure	Female: MSP–RPP	Male: MSP–RAIR
RERI (95% CI)	177.90 (− 12.58 to 678.23)	−15.58 (− 110.48 to 4.07)
AP (95% CI)	83.3% (− 15.9% to 95.6%)	not interpretable (see footnote)
Synergy index S (95% CI)	6.14 (0.86–23.85)	0.31 (0.05–1.39)
Multiplicative interaction OR (95% CI); *P*	0.72 (0.05–11.13); 0.81	0.12 (0.02–0.87); 0.025

RERI, relative excess risk due to interaction; AP, attributable proportion due to interaction. For MSP–RAIR in men, the AP (= RERI/R_{11}) was not interpretable because the joint relative risk ($R_{11} = 7.93$) was small relative to the negative RERI, yielding a point estimate (− 196.3%) outside the interpretable 0–100% range with an extremely wide confidence interval; the RERI and synergy index should be referred to instead.

In men, all quantitative measures consistently indicated antagonism (Table 6): *S* was 0.31 (95% CI 0.05–1.39), RERI was − 15.58 (95% CI − 110.48 to 4.07), and a significant negative multiplicative interaction was observed (interaction OR 0.12, 95% CI 0.02–0.87, $P = 0.025$). The AP was not interpretable in men: with a small joint relative risk ($R_{11} = 7.93$) and a negative RERI, the point estimate (− 196.3%) fell outside the interpretable 0–100% range of an attributable proportion (see Table 6 footnote).

Combined functional (3D HR-ARM) phenotyping and concomitant anatomical classification (defecography) for ERP

Subtype I. ERP with rectocele (Fig. 2A). Variant subtype: a female patient exhibited the R00 phenotype (concurrent normal MSP and RPP); isobaric contour maps demonstrated elevated pressures during

squeeze and bear-down. Defecography: (i) rectal wall defect marked by red dashed lines during lifting; (ii) residual barium indicating rectocele depth during straining (green arrow); and (iii) ERP mucosal imaging during defecation (yellow arrow).

Subtype II. ERP with pelvic floor hernia/internal rectal intussusception (Fig. 2B): a male patient presented the R_{11} phenotype (concurrent reduction of MSP and RAIR); isobaric maps revealed hypotonicity across all phases. Defecography: (i) rectal hypokinesia during lifting; and (ii) ERP mucosal imaging (yellow arrow) and hernia (green arrow) during defecation. Variant subtype: a female patient displayed the R_{01} phenotype (reduced RPP with preserved MSP, Fig. 2C).

Subtype III. ERP with sacrum–rectal separation (Fig. 2D): a male patient showed the R_{11} phenotype. Defecography: sacrum–rectal distance ≥ 20 mm during defecation (double red arrows).

Subtype IV. ERP with megarectum (Fig. 2E): a male patient exhibited the R_{11} phenotype. Defecography: (i) resting rectal diameter ≥ 60 mm (green arrow); (ii) persistent hypokinesia across all phases; and (iii) ERP mucosal imaging during defecation (yellow arrow).

Subtype V. ERP with puborectalis hypertrophy (Fig. 2F). Variant subtype: a male patient displayed the R_{00} phenotype; isobaric maps showed the "hourglass sign" during squeeze [9]. Defecography: the "shelf sign" [22] during straining (green arrow) and ERP mucosal imaging during defecation (yellow arrow).

ROC curve analysis

Receiver operating characteristic (ROC) analysis of the raw continuous measurements (Table 7; Figs. 3 and 4) showed that, in women, MSP alone (cut-off 113.2 mmHg) yielded an AUC of 0.874 (95% CI 0.812–0.927; sensitivity 73.9%, specificity 87.5%) and RPP alone (cut-off 26.0 mmHg) an AUC of 0.858 (95% CI 0.791–0.913; sensitivity 63.8%, specificity 95.8%), and the combined MSP + RPP logistic model further improved discrimination (AUC 0.938, 95% CI 0.896–0.972; sensitivity 92.8%, specificity 86.1%).

Table 7
Discriminative performance of 3D HR-ARM parameters and interaction phenotypes (ERP vs. HVs)

Parameters	Cut-off	Sensitivity	Specificity	Youden index	AUC (95% CI)	*P*
Female						
MSP	113.2 mmHg	73.9% (51/69)	87.5% (63/72)	0.61	0.874 (0.812–0.927)	< 0.001
RPP	26.0 mmHg	63.8% (44/69)	95.8% (69/72)	0.60	0.858 (0.791–0.913)	< 0.001
MSP + RPP combined model	—	92.8% (64/69)	86.1% (62/72)	0.79	0.938 (0.896–0.972)	< 0.001
R_{11} phenotype (MSP–RPP)	—	50.7% (35/69)	98.6% (71/72)	0.49	—	—
Male						
MSP	150.0 mmHg	54.1% (53/98)	85.7% (60/70)	0.40	0.719 (0.641–0.790)	< 0.001
RAIR	Absent RAIR (0 mL)	35.7% (35/98)	100% (70/70)	0.36	0.644 (0.558–0.723)	< 0.001
MSP + RAIR combined model	—	71.4% (70/98)	67.1% (47/70)	0.39	0.731 (0.647–0.804)	< 0.001
R_{11} phenotype (MSP–RAIR)	—	31.6% (31/98)	88.6% (62/70)	0.20	—	—

In men, performance was more modest: MSP alone (cut-off 150.0 mmHg) yielded an AUC of 0.719 (95% CI 0.641–0.790; sensitivity 54.1%, specificity 85.7%), RAIR absence (0 mL) yielded an AUC of 0.644 (95% CI 0.558–0.723; sensitivity 35.7%, specificity 100%), and the combined MSP + RAIR model yielded an AUC of 0.731 (95% CI 0.647–0.804; sensitivity 71.4%, specificity 67.1%). AUC confidence intervals were bootstrap-derived (20,000 resamples). Thus, the combined phenotypic model provided excellent discrimination in women, whereas in men RAIR absence served as a highly specific rule-in sign despite limited overall accuracy.

Discussion

This study is the first to apply sex-stratified interaction analysis of 3D HR-ARM parameters to functional phenotyping of ERP. Two divergent patterns emerged. In women, the R_{11} phenotype (concomitant

reduction of MSP and RPP) carried by far the highest odds of ERP, and the joint effect of the two parameters was super-additive, suggesting that rectal propulsive failure and sphincteric weakness reinforce each other in female ERP. In men, reduced MSP with preserved RAIR (R_{10}) carried the highest odds, and the MSP–RAIR interaction was antagonistic, indicating that MSP reduction is the dominant functional marker of male ERP whereas RAIR impairment adds little—and may even attenuate—the association. These interaction estimates were statistically robust in men (significant negative multiplicative interaction, $P = 0.025$) but exploratory in women, given the small number of controls in the R_{11} phenotype. As a rule-in marker, R_{11} was highly specific (98.6% in women, 88.6% in men) for distinguishing ERP patients from healthy volunteers. The integrated 3D HR-ARM and defecography classification further enabled anatomical–functional mapping of concomitant abnormalities.

In female ERP, reduced MSP may indicate impaired anal sphincter and pelvic floor muscle function, whereas low RPP suggests diminished intrinsic rectal propulsive force. The super-additive interaction observed in the R_{11} phenotype is compatible with a self-reinforcing mechanism: insufficient rectal propulsion leads to repeated straining, chronically elevated abdominal pressure stretches pelvic floor tissues and may damage the pudendal nerve, and the resulting sphincteric weakness further aggravates obstructed evacuation [23–25]. Structural relaxation of the pelvic floor (e.g., after childbirth and with aging) decreases MSP [23], and insufficient rectal support is associated with prolapse progression and a higher proportion of patients with low MSP [24]. This may be related to the weakened supportive effect of estrogen on pelvic floor muscles, consistent with reports of pelvic floor degradation in parous women [3]. A sustained decrease in MSP may exacerbate sphincteric dysfunction, and abnormal rectal sensory thresholds (possibly associated with RPP) may disorder the defecation reflex, creating a pathophysiological vicious cycle of "low anorectal pressure with high abdominal-pressure compensation" that contributes to fecal incontinence, constipation, or their alternation.

In male ERP, MSP reduction emerged as the dominant functional abnormality, and the MSP–RAIR interaction was antagonistic. Reduced MSP reflects abnormal external anal sphincter and pelvic floor muscle tension during voluntary contraction, which may stem from long-term compensatory over-contraction or coordination disorders. Fecal incontinence affects 50%–75% of patients with rectal prolapse and constipation 25%–50% [3]; incontinence may result from sphincteric distortion by the prolapsed tissue, chronic stretch injury, and altered RAIR sensitivity [26]. Weakening or absence of RAIR may indicate abnormal nerve conduction (e.g., pudendal nerve injury) or fibrosis and loss of elasticity of the internal anal sphincter [27]. Park et al. reported absent or impaired RAIR as a marker of high-grade (III–V) rectal prolapse, with impairment correlated with prolapse severity [7]. The antagonistic interaction observed here suggests that, in men, RAIR impairment and MSP reduction may partly reflect a common neuromuscular injury rather than independent additive insults—for example, pudendal nerve injury could simultaneously blunt the reflex and weaken squeeze—so that their co-occurrence conveys little additional risk beyond reduced MSP alone.

ERP is a pelvic floor disorder driven by interactions between structural abnormalities and functional dysfunction. Early recognition of high-risk functional phenotypes—integrating 3D HR-ARM findings with

defecography-based classification of concomitant anatomical abnormalities—may support individualized clinical decision-making. The traditional Oxford Prolapse Scale [19] and Pescatori classification [28] focus solely on prolapse severity and neglect the interaction between concomitant anatomical abnormalities and anorectal dysfunction. Subtype-oriented treatments have been reported for the concomitant abnormalities mapped in this study—for example, transvaginal rectocele repair for concomitant rectocele [29, 30], full pelvic reconstruction (e.g., sacrocolpopexy) for concomitant uterine or bladder prolapse [31], laparoscopic total colectomy with ileorectal intussusception anastomosis for slow-transit constipation confirmed by high-resolution colonic manometry [32], the Jinling procedure for mixed-type constipation [33], and sacral neuromodulation [34] or botulinum toxin injection [35] for puborectalis hypertrophy—but selecting among them on the basis of the present phenotyping system requires prospective validation.

This retrospective observational case–control study had several limitations. Firstly, the retrospective design and the inclusion of only surgical patients, who may not fully represent the entire ERP population, could introduce selection bias. Secondly, subgroup analyses were limited by small sample sizes after stratification (e.g., only one female control in the R_{11} phenotype), which yielded wide confidence intervals for the interaction estimates; the study-derived dichotomization thresholds also risk overfitting and require external validation. Thirdly, although age and BMI were recorded, other potential confounders, such as female reproductive and obstetric history, were not documented. Fourthly, because controls were healthy volunteers, the reported specificity reflects discrimination from healthy individuals rather than from clinically relevant differential diagnoses (e.g., internal rectal intussusception or dyssynergic defecation). Lastly, the absence of postoperative recurrence and functional outcome data precludes evaluation of the prognostic value of the model. The unexpectedly long squeeze durations recorded in female ERP patients (up to 257.9 s) are unlikely to represent continuous maximal voluntary contractions and may reflect sustained paradoxical contraction of the pelvic floor, a hallmark of dyssynergic defecation commonly associated with ERP; this warrants verification with synchronized defecography or EMG in future studies. Future studies should use prospective cohort designs and multiparameter comparisons (endoluminal ultrasonography and pelvic floor electromyography) to validate these findings.

Conclusions

This study introduces a sex-stratified interaction analysis of 3D HR-ARM parameters in ERP. In women, the R_{11} phenotype (concomitant MSP and RPP reduction) identifies patients with the most severe functional impairment through a super-additive joint effect; in men, MSP reduction is the dominant indication, with RAIR impairment showing an antagonistic interaction. As highly specific rule-in markers, these interaction phenotypes, integrated with defecography-based anatomical classification, shift the preoperative evaluation of ERP from static anatomical assessment toward dynamic functional quantification and may inform individualized surgical planning. Prospective, multicenter validation in clinically relevant populations is required before this framework can be adopted in routine practice.

Declarations

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Author contributions

Hong Zhi Geng and Li Li contributed equally to this work. Hong Zhi Geng: study conception and design, data analysis, and drafting of the manuscript. Li Li: data collection and analysis. Chen Xu and Jiying Cong: data collection and critical revision. Hongzhang Liu and Yuwei Li: supervision and critical revision of the manuscript. All authors read and approved the final manuscript.

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Data availability

The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This retrospective study was approved by the Ethics Committee of Tianjin Union Medical Center, Tianjin Institute of Coloproctology, The First Affiliated Hospital of Nankai University, China (approval No. 2024B134). Written informed consent was obtained from all healthy volunteers; for ERP patients, the requirement for individual informed consent was waived by the Ethics Committee owing to the retrospective design and the use of anonymized pre-existing clinical data.

Consent for publication

Written informed consent for publication of the clinical images was obtained from the patients.

Competing interests

The authors declare no competing interests.

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Figures

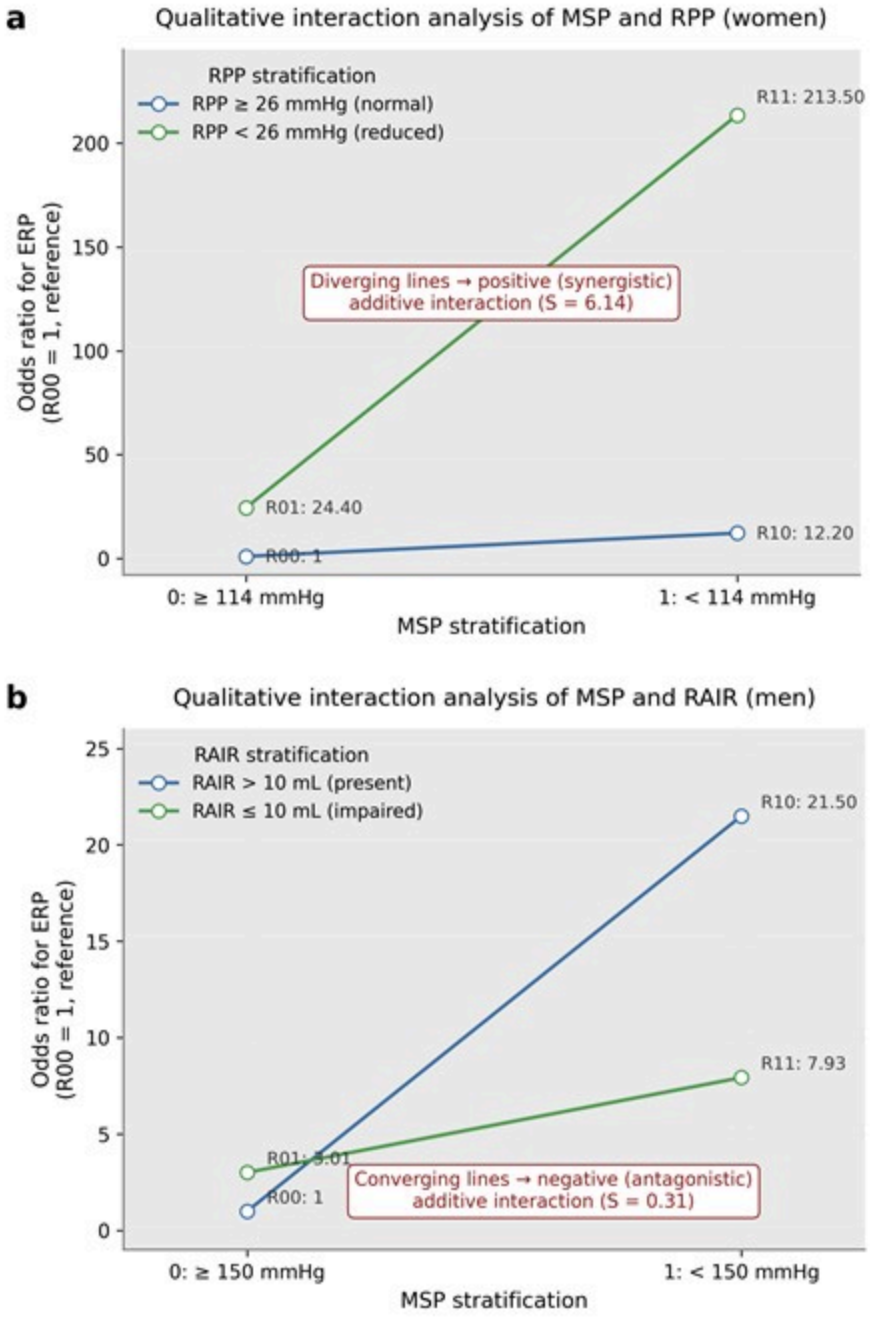


Figure 1

Qualitative interaction analysis of phenotype-specific odds ratios (ORs) for external rectal prolapse (ERP), with R00 (both parameters normal) as the reference (OR = 1). a Women (n = 69 ERP, 72 healthy volunteers): maximum squeeze pressure (MSP) × rectal push pressure (RPP); the diverging lines indicate a positive (synergistic) additive interaction (synergy index *S* = 6.14). b Men (n = 98 ERP, 70 healthy volunteers): MSP × rectoanal inhibitory reflex (RAIR); the converging lines indicate a negative (antagonistic) additive interaction (*S*= 0.31).

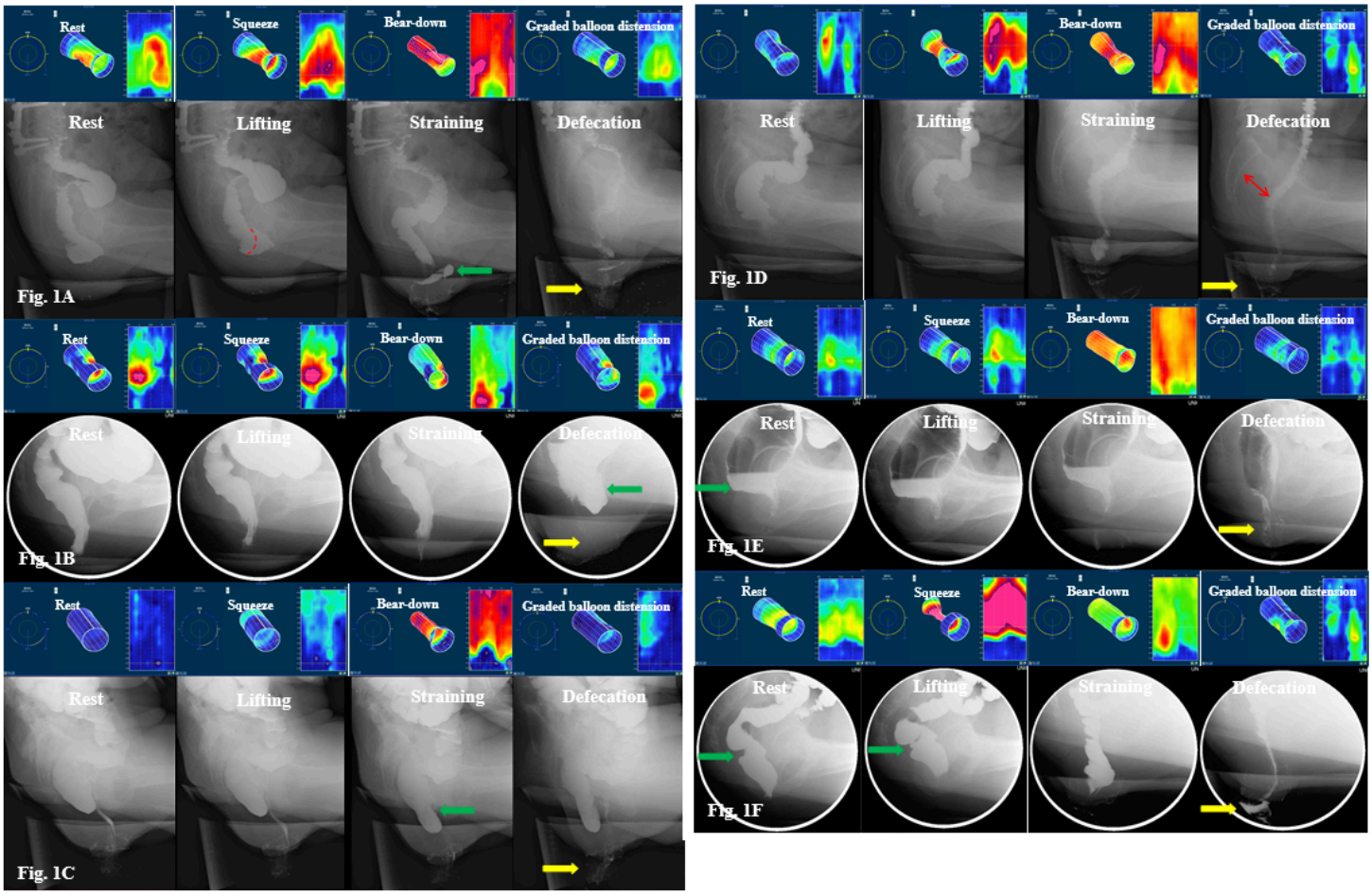


Figure 2

Representative defecography and 3D HR-ARM isobaric contour images of the ERP subtypes. A: subtype I, ERP with rectocele; B: subtype II, ERP with pelvic floor hernia/internal rectal intussusception; C: variant of subtype II (female patient, reduced RPP with preserved MSP); D: subtype III, ERP with sacrum–rectal separation; E: subtype IV, ERP with megarectum; F: subtype V, ERP with puborectalis hypertrophy.

Figure 2A Subtype I. ERP with rectocele. Variant Subtype: 3D HR-ARM: A female patient exhibited the R00 phenotype (normal MSP and RPP). Isobaric contour maps demonstrate elevated pressures during squeeze and bear-down. Defecography: (□) Rectal wall defect marked by red dashed lines during lifting, (□) Residual barium indicates rectocele depth during straining (green arrow), and (□) During defecation shows ERP mucosal imaging (yellow arrow).

Figure 2B Subtype II. ERP with pelvic floor hernia/internal rectal intussusception/splanchnoptosis. 3D HR-ARM: A male patient presented the R11 phenotype (concurrent reduction MSP-RAIR). Isobaric maps reveal hypotonicity across all phases. Defecography: (□) Rectal hypokinesia during lifting, and (□) During defecation demonstrates ERP mucosal imaging (yellow arrow) and hernia (green arrow).

Figure 2C Subtype II. ERP with pelvic floor hernia/splanchnoptosis. Variant Subtype: 3D HR-ARM: A female patient displayed the R01 phenotype (reduced RPP with preserved MSP).

Figure 2D Subtype III. ERP with sacrum-rectal separation. 3D HR-ARM: A male patient showed the R11 phenotype (concurrent reduction MSP-RAIR). Defecography: Sacrum-rectal distance ≥20 mm during defecation (double red arrows).

Figure 2E Subtype IV. ERP with megarectum. 3D HR-ARM: A male patient exhibited the R11 phenotype (concurrent reduction MSP-RAIR). Defecography: (□) Resting rectal diameter ≥60 mm (green arrow), (□) Persistent hypokinesia across all phases, and (□) During defecation demonstrates ERP mucosal imaging (yellow arrow),

Figure 2F Subtype V. ERP with puborectalis hypertrophy. Variant Subtype: 3D HR-ARM: A male patient display R00 phenotype (concurrent elevation MSP-RAIR). Isobaric maps show "hourglass sign" during squeeze 9. Defecography: "Shelf sign"22 (green arrow) from markings during straining. During defecation shows ERP mucosal imaging (yellow arrow).

Defecography-based classification of ERP-concomitant diseases can be identified using 3D HR-ARM phenotypes, but not vice versa. The combination of these two modalities has potential for guiding personalized therapeutic strategies.

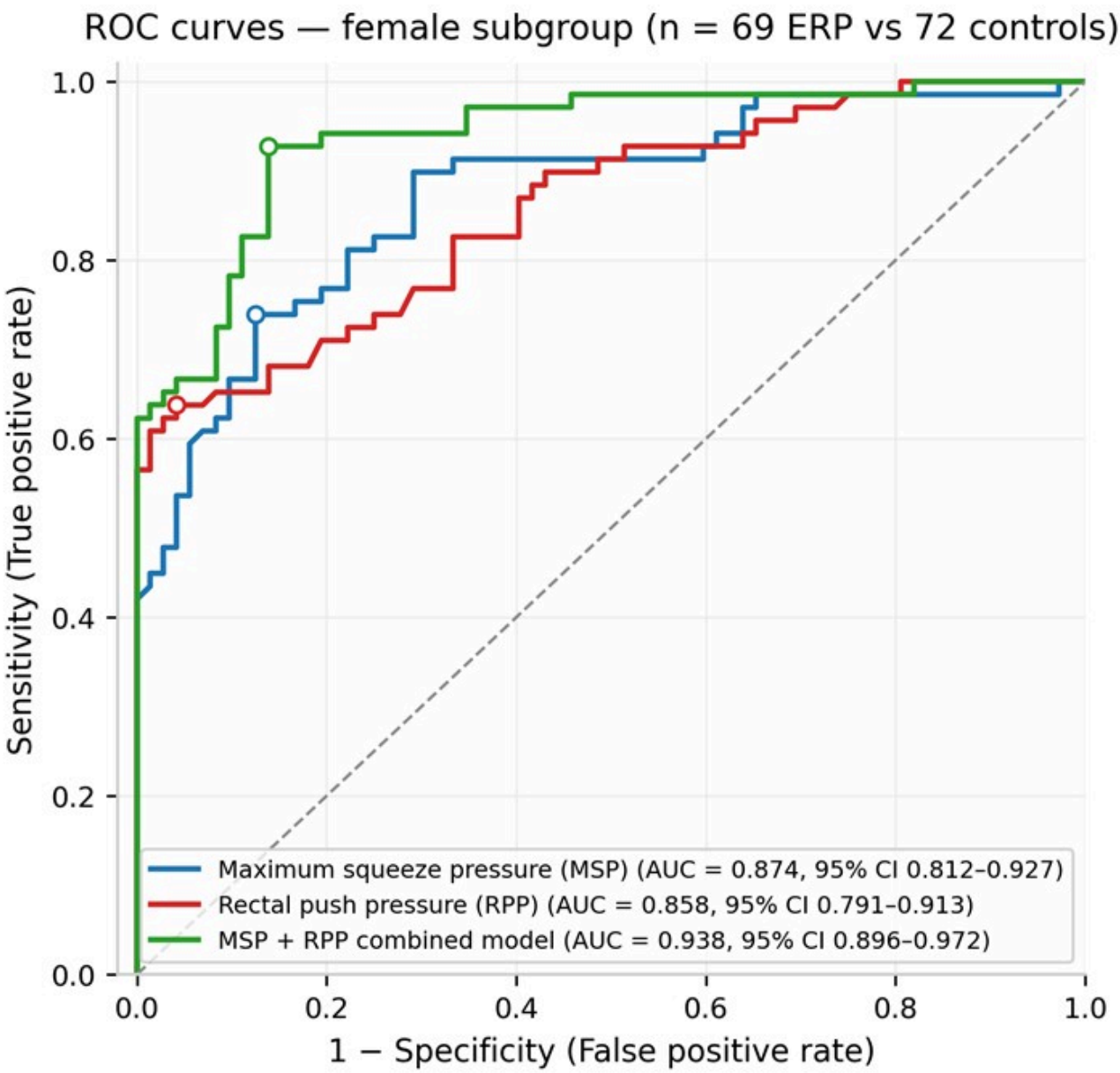


Figure 3

Receiver operating characteristic curves for maximum squeeze pressure (MSP), rectal push pressure (RPP), and the combined MSP + RPP logistic model in the female subgroup (69 ERP patients vs. 72 healthy volunteers).

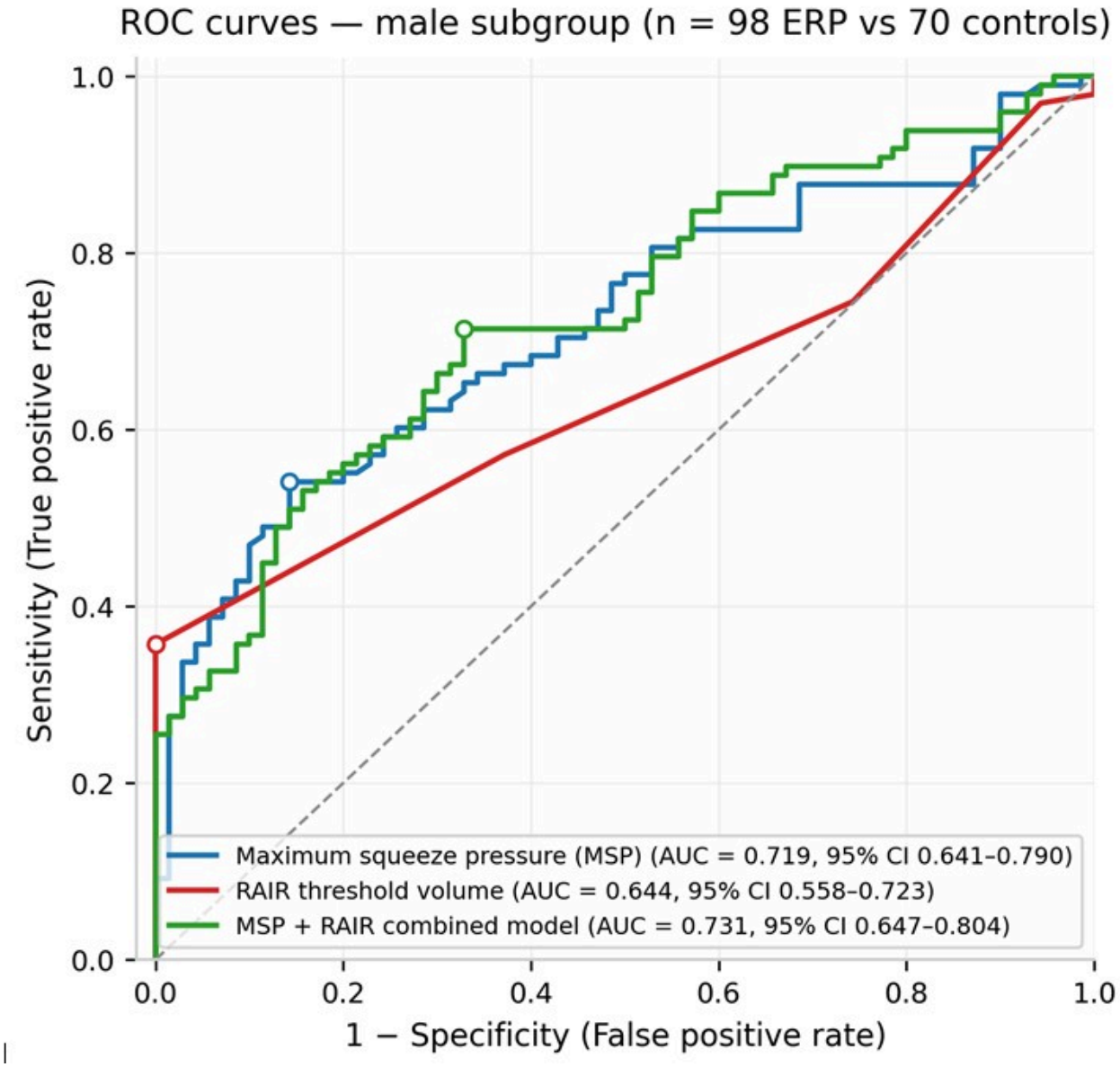


Figure 4

Receiver operating characteristic curves for maximum squeeze pressure (MSP), the rectoanal inhibitory reflex (RAIR) threshold, and the combined MSP + RAIR logistic model in the male subgroup (98 ERP patients vs. 70 healthy volunteers).

Supplementary Files

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- SupplementaryTableS1..doc
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