

Routine Postoperative Biomarkers for Early Detection of Anastomotic Leakage After Hartmann's Reversal: A Comparative Study

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Abstract

Background

Anastomotic leakage (AL) remains one of the most clinically relevant complications after Hartmann's reversal (HR). Although C-reactive protein (CRP) is widely used for postoperative surveillance after colorectal surgery, the comparative performance of routinely available inflammatory biomarkers specifically after HR remains insufficiently characterized.

Methods

We conducted a retrospective single-center cohort study including 86 adult patients undergoing elective Hartmann's reversal with colorectal anastomosis. The primary outcome was clinically relevant AL. CRP, C-reactive protein-to-albumin ratio (CAR), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) were evaluated on postoperative days (POD) 1, 3, and 5. Discrimination was assessed using receiver operating characteristic curves and areas under the curve (AUCs) with 95% confidence intervals. Exploratory cutoffs were determined using the Youden index. Pairwise AUC comparisons used the DeLong method in patients with paired measurements, and univariable logistic regression quantified associations with AL.

Results

AL occurred in 9 of 86 patients (10.5%). On POD3, PLR showed the highest observed AUC (0.882), followed by NLR (0.835), CAR (0.827), and CRP (0.793). A PLR cutoff ≥ 358.33 yielded 66.7% sensitivity, 96.9% specificity, and 95.5% negative predictive value (NPV), whereas NLR ≥ 7.75 yielded 88.9% sensitivity, 75.0% specificity, and 98.0% NPV. No statistically significant differences were identified in direct pairwise DeLong comparisons. Each 100-unit increase in POD3 PLR was associated with higher odds of AL (OR 4.44, 95% CI 1.76–11.23), as was each 5-unit increase in NLR (OR 2.41, 95% CI 1.35–4.29).

Conclusions

Routine postoperative inflammatory biomarkers demonstrated clinically relevant discrimination for AL after Hartmann's reversal, particularly on POD3. PLR showed the highest observed AUC, while NLR, CAR, and CRP demonstrated comparable discrimination without statistically significant superiority of any individual biomarker. The derived thresholds require external validation before clinical implementation.

Introduction

Hartmann's reversal (HR) is a technically demanding reconstructive procedure associated with substantial postoperative morbidity. Anastomotic leakage (AL), although relatively infrequent, is among its most clinically consequential complications. Contemporary Hartmann reversal series report AL rates of approximately 3–4%, while broader morbidity remains substantial [1–4]. Early identification of AL is important because clinical manifestations may be subtle or nonspecific during the initial postoperative period.

Among routinely available laboratory parameters, C-reactive protein (CRP) is the most extensively studied biomarker for early detection of AL after colorectal surgery. Serial postoperative measurements appear particularly informative, with discriminatory performance generally improving after the first postoperative days. Meta-analytic and prospective evidence supports CRP, particularly from POD3 onward, as an adjunct for identifying patients at low or increased likelihood of AL [5–7].

The C-reactive protein-to-albumin ratio (CAR) integrates the acute inflammatory response represented by CRP with changes in serum albumin. In a multicenter cohort of 1,183 patients undergoing colorectal cancer surgery, postoperative CAR

demonstrated good discriminatory ability for AL (AUC 0.825) and performed better than CRP or albumin individually [8]. Similarly, NLR and PLR can be calculated directly from routine complete blood counts and have been investigated as early indicators of leakage. In a multicenter cohort of 1,432 patients, postoperative blood-cell-derived inflammatory indices were higher among patients who developed AL [9]. However, comparative findings have not been uniform, and CRP has outperformed NLR in some cohorts [10].

Despite growing evidence supporting CRP, CAR, NLR, and PLR after colorectal surgery, their comparative discriminatory performance specifically after Hartmann's reversal remains insufficiently characterized. Therefore, the primary objective of this study was to compare CRP, CAR, NLR, and PLR measured on POD1, POD3, and POD5 for early detection of AL after Hartmann's reversal. Secondary objectives were to identify the postoperative time point at which each biomarker achieved its greatest discrimination and to compare AUCs directly using paired analyses.

Materials and Methods

Study design and population

This retrospective, single-center cohort study was conducted at the Department of Coloproctology, Hospital General de México "Dr. Eduardo Liceaga", Mexico City, Mexico. It included adult patients who underwent elective Hartmann's reversal with colorectal anastomosis between April 2019 and March 2025. The final cohort comprised 86 patients. Patients were eligible if they were ≥ 18 years of age, underwent elective restoration of intestinal continuity with a colorectal anastomosis, and had sufficient clinical and postoperative follow-up to determine AL. Patients undergoing coloanal, ileorectal, or ileoanal anastomosis, emergency surgery, or restoration in the presence of active sepsis or peritonitis were excluded. Demographic, operative, laboratory, and postoperative outcome data were obtained retrospectively from institutional clinical records and the study database. The study was prepared in accordance with STROBE recommendations [11]. A previously published study from our institution evaluated postoperative CRP kinetics and overall surgical outcomes after Hartmann's reversal [16]. The present investigation is a separate study with a distinct research question and analytical cohort; it was not conducted as a sub-study of that work. Here, the primary outcome is anastomotic leakage and the analysis directly compares CRP, CAR, NLR, and PLR across POD1, POD3, and POD5.

Outcome definition

The primary outcome was clinically relevant anastomotic leakage after Hartmann's reversal. AL was defined as a defect in the integrity of the intestinal wall at the colorectal anastomotic site resulting in clinically, radiologically, or surgically relevant consequences, consistent with the International Study Group of Rectal Cancer definition [12]. Clinically relevant grade B and grade C leaks were considered events for the primary analysis.

Laboratory measurements and biomarker calculation

Routine laboratory tests were obtained as part of standard postoperative care and were categorized as POD1, POD3, and POD5 measurements. NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count, and PLR by dividing the platelet count by the absolute lymphocyte count. CAR was calculated as CRP (mg/L) divided by serum albumin (g/dL) measured at the corresponding postoperative time point. No biomarker values were imputed. Blank cells, dashes, isolated punctuation marks, and other nonnumeric entries were treated as missing rather than as zero values.

Statistical analysis

The distribution of continuous variables was assessed using the Shapiro-Wilk test. Normally distributed variables are reported as mean $\pm$ standard deviation, whereas non-normally distributed variables are reported as median and interquartile range. Between-group comparisons were performed using Student's t test or the Mann-Whitney U test, as appropriate.

Categorical variables were compared using the chi-square test or Fisher's exact test. Receiver operating characteristic (ROC) analyses were performed separately for CRP, CAR, NLR, and PLR on POD1, POD3, and POD5, and areas under the curve (AUCs) were reported with 95% confidence intervals. Exploratory optimal cutoffs were identified using the Youden index [13]; sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated at each cutoff. Pairwise AUC comparisons were restricted to patients with both biomarkers available at the same postoperative time point and were performed using the DeLong method [14]. Univariable logistic regression was used to quantify associations with AL using clinically interpretable increments of 5 units for NLR, 100 units for PLR, 50 mg/L for CRP, and 10 units for CAR. Given the occurrence of only nine AL events, extensive multivariable modeling was deliberately avoided to minimize overfitting. Analyses were based on available cases for each biomarker and time point, with no imputation of missing laboratory values. All tests were two-sided, and $p < 0.05$ was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics, version 32.0 (IBM Corp., Armonk, NY, USA).

Ethics statement

The study was reviewed by the institutional ethics committee of Hospital General de México “Dr. Eduardo Liceaga”. Given its retrospective design and use of de-identified routinely collected clinical data, the committee determined that the study could proceed without assignment of a formal approval number. The requirement for individual informed consent for participation was considered not applicable for this retrospective analysis. The study was conducted in accordance with the Declaration of Helsinki, and patient confidentiality was preserved throughout.

Results

Study cohort and temporal biomarker performance

A total of 86 patients were included, of whom 9 (10.5%) developed AL. Baseline demographic and operative characteristics were similar between patients with and without AL, with no statistically significant differences in age, BMI, sex, operative time, estimated blood loss, surgical approach, or preoperative albumin (Table 1). All colorectal anastomoses were mechanically constructed. Median length of stay was longer in patients with AL (9 vs 7 days), although this difference was not statistically significant ($p = 0.098$). Biomarker availability varied across postoperative time points; therefore, analyses were performed using available cases without imputation.

Table 1
Baseline and perioperative characteristics according to anastomotic leakage.

Characteristic	AL (n = 9)	No AL (n = 77)	p value
Age, years	53.00 (41.00–61.00)	48.00 (41.00–60.00)	0.544
BMI, kg/m ²	26.80 (25.33–28.00)	25.70 (24.20–27.40)	0.167
Operative time, min	175.00 (170.00–227.00)	184.00 (150.00–240.00)	0.799
Estimated blood loss, mL	150.00 (50.00–200.00)	100.00 (50.00–200.00)	0.699
Length of stay, days	9.00 (6.00–11.00)	7.00 (6.00–8.00)	0.098
Preoperative albumin, g/dL	4.60 (4.10–4.78)	4.41 (4.17–4.72)	0.735
Male sex	6 (66.7%)	44 (57.1%)	0.729
Laparoscopic approach	7 (77.8%)	46 (59.7%)	0.472
Data are median (IQR) or n (%). Continuous variables were compared using the Mann–Whitney U test; categorical variables using Fisher’s exact test. Postoperative outcomes such as reintervention and readmission are not included as baseline predictors. All colorectal anastomoses in the cohort were mechanically constructed.			

POD3 diagnostic performance

At the exploratory POD3 cutoff of $\text{PLR} \geq 358.33$, sensitivity was 66.7%, specificity 96.9%, PPV 75.0%, and NPV 95.5%. $\text{NLR} \geq 7.75$ yielded 88.9% sensitivity, 75.0% specificity, 33.3% PPV, and 98.0% NPV. $\text{CRP} \geq 201$ mg/L yielded 85.7% sensitivity, 68.3% specificity, 24.0% PPV, and 97.6% NPV. $\text{CAR} \geq 70.61$ yielded 83.3% sensitivity, 82.1% specificity, 50.0% PPV, and 95.8% NPV.

Pairwise AUC comparisons and univariable associations

Although PLR had the highest observed POD3 AUC, none of the pairwise DeLong comparisons showed a statistically significant difference between biomarkers. Univariable logistic regression further supported the POD3 associations. The odds of AL increased by 4.44-fold for each 100-unit increase in PLR (95% CI 1.76–11.23; $p = 0.0016$), 2.41-fold for each 5-unit increase in NLR (95% CI 1.35–4.29; $p = 0.0029$), 1.87-fold for each 50-mg/L increase in CRP (95% CI 1.11–3.16; $p = 0.0195$), and 1.44-fold for each 10-unit increase in CAR (95% CI 1.05–1.98; $p = 0.0233$).

Table 2
Diagnostic performance of postoperative biomarkers for anastomotic leakage.

POD	Marker	n	AL	Median AL	Median no AL	p	AUC (95% CI)	Cutoff	Sens.	Spec.	PPV	NPV
POD1	CAR	34	4	29.41	24.39	0.453	0.625 (0.420–0.830)	18.51	100.0%	43.3%	19.0%	100.0%
POD1	NLR	73	9	12.62	11.68	0.265	0.616 (0.445–0.787)	10.27	88.9%	45.3%	18.6%	96.7%
POD1	PLR	74	9	287.50	259.81	0.268	0.615 (0.407–0.824)	445.59	44.4%	83.1%	26.7%	91.5%
POD1	CRP	72	7	86.19	82.89	0.530	0.574 (0.370–0.777)	57.04	100.0%	30.8%	13.5%	100.0%
POD3	PLR	74	9	393.33	167.69	< 0.001	0.882 (0.748–1.000)	358.33	66.7%	96.9%	75.0%	95.5%
POD3	NLR	73	9	14.35	4.57	0.001	0.835 (0.674–0.996)	7.75	88.9%	75.0%	33.3%	98.0%
POD3	CAR	34	6	88.75	49.26	0.011	0.827 (0.630–1.000)	70.61	83.3%	82.1%	50.0%	95.8%
POD3	CRP	67	7	246.44	161.96	0.012	0.793 (0.643–0.943)	201.00	85.7%	68.3%	24.0%	97.6%
POD5	CRP	54	5	213.26	88.10	0.014	0.837 (0.667–1.000)	135.22	80.0%	77.6%	26.7%	97.4%
POD5	NLR	58	8	13.32	4.14	0.010	0.789 (0.553–1.000)	5.86	87.5%	70.0%	31.8%	97.2%
POD5	PLR	60	9	314.55	200.69	0.027	0.734 (0.506–0.962)	247.65	77.8%	70.6%	31.8%	94.7%
POD5	CAR	14	2	49.92	36.00	0.659	0.625 (0.027–1.000)	74.05	50.0%	91.7%	50.0%	91.7%

Bold AUC values indicate the highest observed AUC at each postoperative time point. Cutoffs were derived using the Youden index and should be considered exploratory. POD, postoperative day; AL, anastomotic leakage; AUC, area under the curve; Sens., sensitivity; Spec., specificity; PPV, positive predictive value; NPV, negative predictive value.

Table 3
Pairwise DeLong comparisons of POD3 ROC curves.

Comparison	Paired n	AL events	AUC first	AUC second	DeLong p
PLR vs NLR	73	9	0.887	0.835	0.232
PLR vs CAR	34	6	0.845	0.827	0.809
PLR vs CRP	62	7	0.857	0.803	0.446
NLR vs CAR	34	6	0.857	0.827	0.658
NLR vs CRP	61	7	0.823	0.802	0.753
CAR vs CRP	34	6	0.827	0.821	0.694

Table 4
Univariable logistic regression for anastomotic leakage.

POD	Biomarker	n	AL events	Increment	OR	95% CI	p
POD1	NLR	73	9	+ 5	1.09	0.846–1.415	0.4916
POD1	PLR	74	9	+ 100	1.21	0.850–1.710	0.2937
POD1	CRP	72	7	+ 50 mg/L	1.24	0.652–2.347	0.5145
POD1	CAR	34	4	+ 10	1.10	0.632–1.917	0.7352
POD3	NLR	73	9	+ 5	2.41	1.350–4.293	0.0029
POD3	PLR	74	9	+ 100	4.44	1.760–11.225	0.0016
POD3	CRP	67	7	+ 50 mg/L	1.87	1.106–3.161	0.0195
POD3	CAR	34	6	+ 10	1.44	1.051–1.984	0.0233
POD5	NLR	58	8	+ 5	3.03	1.404–6.539	0.0047
POD5	PLR	60	9	+ 100	2.13	1.191–3.799	0.0108
POD5	CRP	54	5	+ 50 mg/L	2.01	1.129–3.594	0.0177
POD5	CAR	14	2	+ 10	1.34	0.663–2.710	0.4155

Discussion

In this retrospective cohort of patients undergoing Hartmann's reversal, the discriminatory performance of routinely available postoperative inflammatory biomarkers varied over time. POD3 was the most informative assessment point overall: PLR had the highest observed AUC, followed by NLR, CAR, and CRP, whereas all four biomarkers showed poor discrimination on POD1. Despite the numerically higher POD3 AUC for PLR, paired DeLong comparisons identified no statistically significant differences among biomarkers. Thus, our findings do not establish the superiority of PLR; rather, they suggest that several routinely available inflammatory markers may provide clinically relevant information by the third postoperative day.

This temporal pattern is consistent with previous colorectal literature. The early systemic inflammatory response to major abdominal surgery may limit biomarker specificity on POD1, whereas persistent or increasing inflammation over subsequent days may more accurately reflect an evolving postoperative complication. Meta-analyses of CRP after colorectal surgery have demonstrated improved diagnostic performance from POD3 onward [5, 6], supporting the existence of a clinically relevant biochemical window before AL becomes clinically apparent.

PLR showed the highest observed discrimination on POD3 (AUC 0.882). The exploratory cutoff of ≥ 358.33 yielded a specificity of 96.9%, a PPV of 75.0%, and an NPV of 95.5%. Similarly, Paliogiannis et al. reported associations between postoperative blood-cell-derived inflammatory indices and AL in 1,432 elective colorectal procedures [9]. However, the favorable performance of PLR in our cohort should be interpreted cautiously because only nine AL events occurred, the cutoff was derived internally, and formal paired AUC comparisons did not demonstrate its superiority over the other biomarkers.

NLR also showed good discriminatory performance on POD3 (AUC 0.835). At a cutoff of ≥ 7.75 , sensitivity was 88.9% and the NPV was 98.0%. Prospective data from Agnello et al. likewise showed higher NLR values among patients with AL on POD3 and POD5 [15]. However, findings across studies are not uniform; Pantoja Pachajoa et al. reported better performance for CRP than for NLR [10]. Differences in patient selection, surgical indication, anastomotic level, timing of postoperative measurements, and AL prevalence may partly account for these discrepancies.

CAR also showed good discrimination on POD3 (AUC 0.827), consistent with the AUC of 0.825 reported by Paliogiannis et al. for postoperative CAR in 1,183 patients undergoing colorectal cancer surgery [8]. However, CAR highlights a practical limitation of composite biomarkers because its calculation requires contemporaneous CRP and albumin measurements. In our cohort, only 34 patients, including six with AL, had sufficient POD3 data to calculate CAR; consequently, this estimate is less precise than those for NLR and PLR.

CRP remained a clinically relevant comparator, with an AUC of 0.793 on POD3 and 0.837 on POD5. These findings are consistent with extensive evidence supporting CRP as a postoperative rule-out marker for AL, particularly from POD3 onward [5–7]. However, the cutoff values identified in the present study should not be regarded as universal clinical thresholds because they were both derived and evaluated within the same cohort.

Another clinically relevant finding was the high NPV of several POD3 biomarkers, supporting their potential use as adjunctive rule-out rather than stand-alone rule-in tools. A low biomarker value in an otherwise clinically stable patient may provide additional reassurance, whereas an elevated value is nonspecific and should be interpreted alongside clinical findings, serial biomarker trends, and imaging when indicated. Because predictive values depend on disease prevalence, the NPVs observed in this cohort should not be extrapolated directly to populations with substantially different baseline risks.

The focus on Hartmann's reversal is both a strength and a limitation. Most biomarker studies include heterogeneous colorectal procedures, whereas our cohort represents a specific reconstructive operation. Recent work in patients undergoing Hartmann's reversal has shown that early CRP kinetics provide prognostic information regarding postoperative surgical outcomes [16]. The present study addresses a distinct question by focusing specifically on AL and directly comparing several routinely available biomarkers at standardized postoperative time points.

From a practical standpoint, NLR and PLR are attractive because both can be calculated from routine complete blood counts without additional testing. CAR also relies on routinely available laboratory measurements but requires postoperative albumin assessment. Given the absence of statistically significant differences between AUCs, future studies should determine whether biomarker combinations or longitudinal trajectories improve discrimination beyond single measurements rather than seeking a single "best" marker.

Strengths and limitations

The main strengths of this study are the evaluation of a well-defined Hartmann's reversal population; assessment of CRP, CAR, NLR, and PLR within the same cohort at standardized POD1, POD3, and POD5 time points; ROC analyses with confidence intervals and exploratory thresholds; clinically interpretable univariable odds ratios; and paired DeLong comparisons. All analyses were performed directly from patient-level data using an available-case approach without imputation.

This study has several limitations. Its retrospective, single-center design, modest sample size of 86 patients, and only nine AL events limit the precision of the estimates and preclude robust multivariable modeling. Biomarker availability was heterogeneous, particularly for postoperative albumin and CAR, and missing laboratory measurements may not have occurred completely at random. POD5 analyses were based on fewer observations. Furthermore, optimal cutoffs were derived and evaluated in the same dataset, and no external validation cohort was available; these thresholds therefore require independent validation before clinical implementation.

Conclusions

Among patients undergoing Hartmann's reversal, the discriminatory performance of routinely available postoperative inflammatory biomarkers varied over time, with POD3 emerging as the most informative assessment point overall. PLR had the highest observed POD3 AUC, followed by NLR, CAR, and CRP; however, paired DeLong comparisons showed no statistically significant superiority of any individual biomarker. The high NPVs observed for several POD3 markers support their potential adjunctive role in postoperative risk stratification. Prospective multicenter studies with external validation are needed before the proposed thresholds can be incorporated into clinical decision-making.

Declarations

Ethics approval and consent to participate: Ethics approval and consent to participate: The studies involving humans were approved by Comité Institucional de Ética e Investigación del Hospital General de México. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because the retrospective nature of the study.

Availability of data and materials: The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request, subject to institutional data-protection requirements.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: D.I.A.G. and A.J.I.J. contributed to the conception and design of the study. J.M.V., J.L.R., B.J.B., A.F.H.T., A.V.T and R.L.H contributed to data collection. J.M.V., B.D., L.O.P., A.F.H.T., A.V.T. and R.L.H contributed to the literature review. D.I.A.G. and B.D. drafted the manuscript. All authors critically revised the manuscript for important intellectual content, read and approved the final version, and agree to be accountable for all aspects of the work. D.I.A.G. is the guarantor of the study.

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Figures

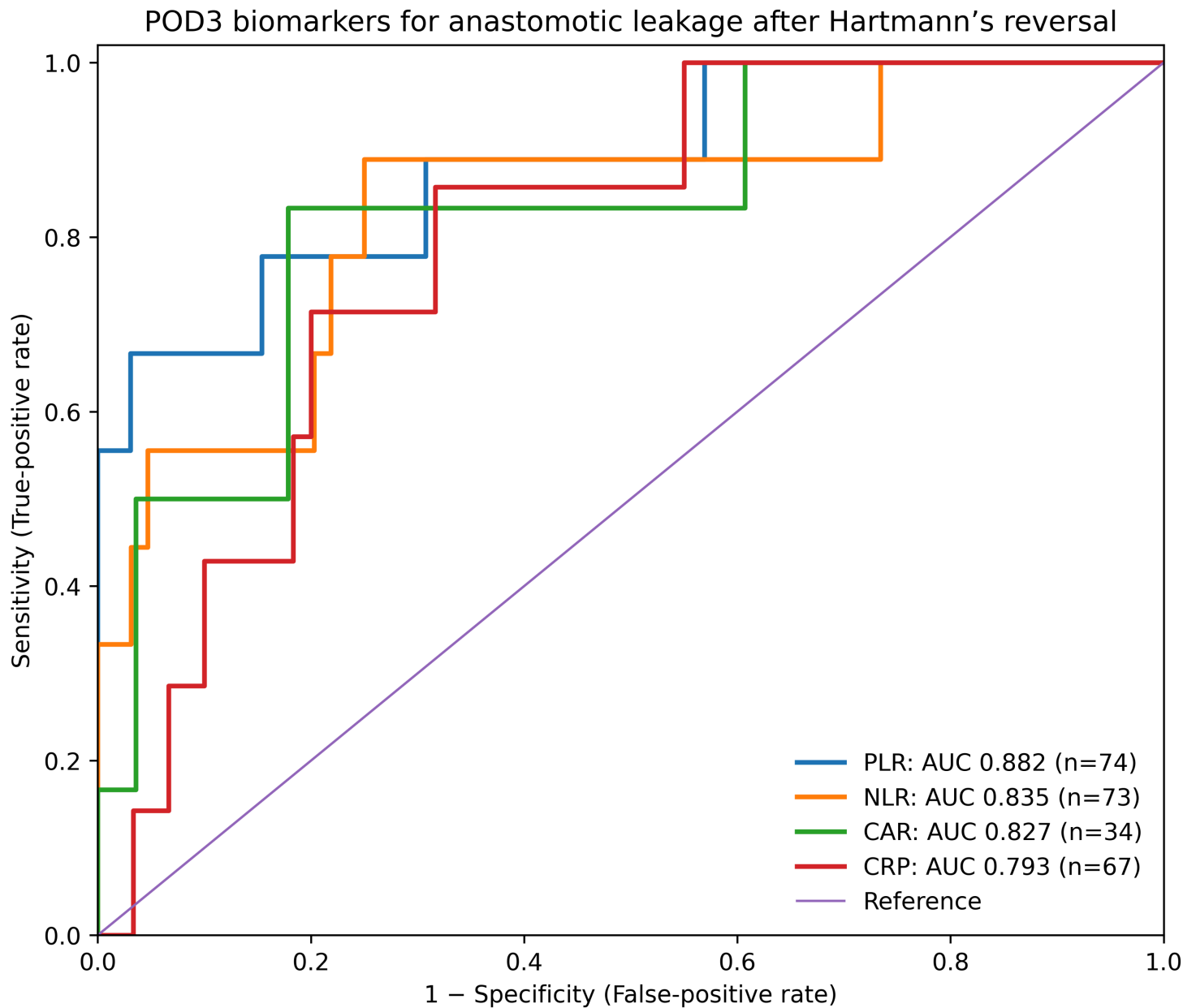


Figure 1

Receiver operating characteristic curves of postoperative day 3 biomarkers for detection of anastomotic leakage after Hartmann's reversal. PLR showed the highest observed discriminatory performance (AUC 0.882), followed by NLR (AUC 0.835), CAR (AUC 0.827), and CRP (AUC 0.793). Pairwise comparisons of AUCs were performed using the DeLong method in patients with paired biomarker measurements.

Figure 2. Forest Plot of Odds Ratios for Anastomotic Leakage According to Biomarker Levels at POD1, POD3 and POD5

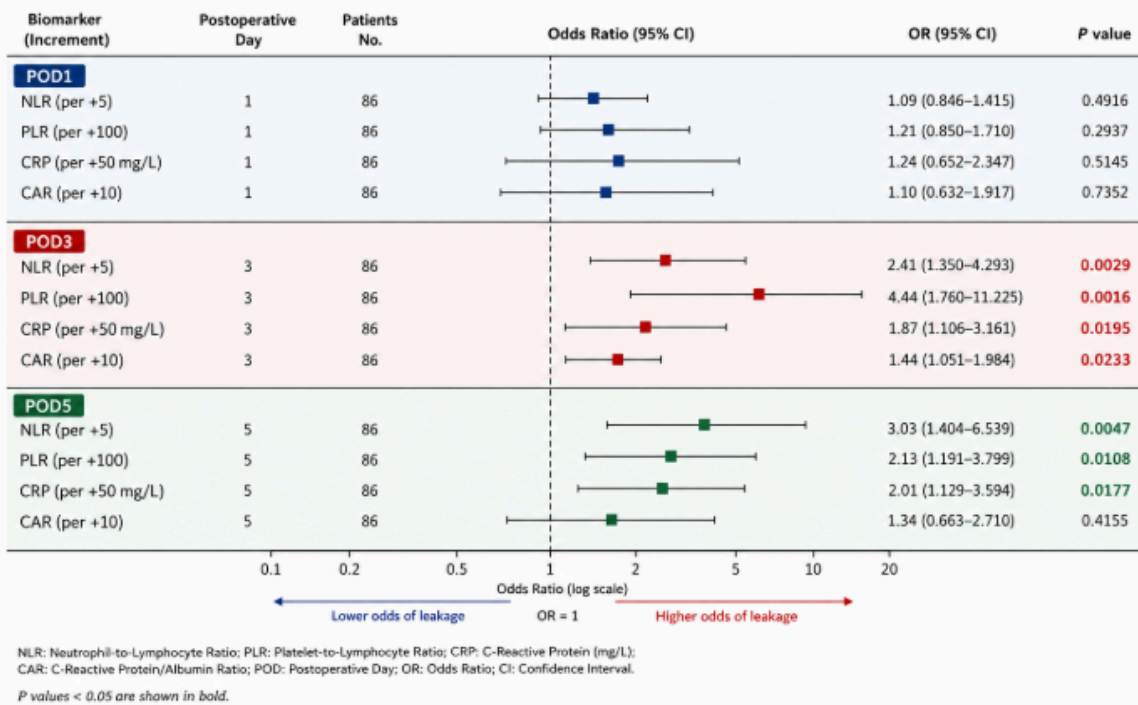


Figure 2

Univariable associations between postoperative biomarkers and anastomotic leakage after Hartmann's. Forest plot showing odds ratios (ORs) and 95% confidence intervals derived from univariable logistic regression. ORs are expressed per prespecified clinically interpretable increment: NLR, +5 units; PLR, +100 units; CRP, +50 mg/L; and CAR, +10 units. The vertical reference line indicates OR = 1; bold P values indicate $P < 0.05$.

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