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Endothelial Biomarkers Predict Clinical Deterioration in Acute Pancreatitis

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ABSTRACT

Objective: Endothelial dysfunction contributes to the severity of acute pancreatitis (AP), but the prognostic utility of endothelial biomarkers and their association with therapeutic interventions remain poorly defined. This study aimed to determine whether endothelial dysfunction biomarkers predict clinical deterioration in AP and whether plasmapheresis is associated with changes in these biomarkers and clinical outcomes.

Materials and Methods: In this prospective cohort study of 100 patients with AP, serial endothelial biomarkers, including vascular endothelial growth factor (VEGF), von Willebrand factor (vWF), endothelin-1 (ET-1), and soluble E-selectin (sE-selectin), were measured on admission and on days 3 and 7. All patients received conventional therapy, and 68 additionally received adjunctive plasmapheresis through nonrandomized assignment. The conventional therapy cohort (n=32) was stratified into Worsened (n=17) and Improved (n=15) subgroups according to clinical course to establish prognostic biomarker cutoffs.

Results: Endothelial marker levels at admission predicted subsequent clinical deterioration ($p<0.001$). Biomarker trajectories differed significantly between the Improved and Worsened subgroups. Patients who received plasmapheresis exhibited more favorable biomarker profiles, with levels resembling those of the Improved subgroup by day 7. This biomarker pattern was associated with a lower rate of the composite clinical deterioration endpoint than that observed in the Worsened subgroup (12% vs. 100%, $p<0.001$).

Conclusion: Endothelial dysfunction biomarkers are early predictors of the clinical course of AP. Plasmapheresis was associated with favorable biomarker trajectories and improved clinical outcomes, suggesting that endothelial dysfunction may be a potential therapeutic target warranting investigation in randomized trials.

Keywords: Acute pancreatitis, biomarkers, endothelial dysfunction, plasmapheresis, prognosis.

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INTRODUCTION

Acute pancreatitis (AP) is an inflammatory disease with a highly variable clinical course, ranging from a mild, self-limited illness to severe disease characterized by persistent organ failure, multiorgan dysfunction, and high mortality.[1] Early identification of patients at risk of clinical deterioration

remains a major challenge because currently available scoring systems have limited predictive accuracy within the first 48–72 hours.[2] Accumulating evidence suggests that endothelial dysfunction may be a central pathophysiological mechanism linking early pancreatic injury to systemic inflammation and organ failure in AP.[3]

Endothelial injury in critical illness is characterized by glycocalyx degradation, increased vascular permeability, and dysregulation of hemostatic pathways.[4] Key biomarkers include von Willebrand factor (vWF), angiopoietin-2, and glycocalyx components.[5] Similar alterations occur in septic shock, inflammatory bowel disease, and hepatic malignancies, in which elevated vWF levels correlate with disease severity.[6–8] Comparable endothelial changes are also thought to occur in severe AP; however, this area remains insufficiently explored.[9]

Recent studies of septic shock—a condition that shares systemic inflammation and microvascular failure with severe AP—have shown that endothelial biomarkers are closely associated with disease severity and may reflect underlying pathophysiological processes.[10] In this context, therapeutic plasma exchange (TPE) has been associated with reductions in circulating mediators and improvements in endothelial markers.[10,11] Although TPE is an established therapy for hypertriglyceridemic pancreatitis, its use in this setting has primarily been directed toward reducing the triglyceride burden.[1] Whether TPE can influence endothelial dysfunction in AP independently of triglyceride reduction remains an important unanswered question. Given the shared pathways of cytokine release, oxidative stress, and microvascular injury in sepsis and severe AP, endothelial dysfunction biomarkers may serve as promising early prognostic indicators.[12] However, two major knowledge gaps remain: (1) the prognostic utility of endothelial dysfunction biomarkers in AP has not been established, and (2) the association between plasmapheresis and changes in the trajectories of these biomarkers in AP is unknown.

The present study aimed to (1) evaluate the ability of endothelial dysfunction biomarkers to predict clinical deterioration in AP and (2) assess whether plasmapheresis is associated with changes in these biomarkers and clinical outcomes.

MATERIALS AND METHODS

Study Setting and Design

This prospective observational cohort study was conducted between 2019 and 2022 at a tertiary surgical center. The study was designed to evaluate the prognostic utility of endothelial dysfunction biomarkers and assess the association between plasmapheresis and biomarker trajectories in patients with acute pancreatitis.

KEY MESSAGES

- Serial endothelial biomarkers—particularly sE-selectin and endothelin-1—strongly predict clinical deterioration in acute pancreatitis, with sE-selectin levels on day 3 demonstrating excellent predictive accuracy (AUC=0.905).
- Plasmapheresis was associated with favorable biomarker trajectories and a significantly lower rate of clinical deterioration (12% vs. 100% in the Worsened subgroup, p<0.001).
- Endothelial dysfunction may represent a modifiable therapeutic target in acute pancreatitis, supporting the need for randomized trials of biomarker-guided interventions.

Ethics Approval

The study protocol was approved by the Academic M.A. Topchubashov Scientific Surgery Center Ethics Committee (Approval Number: 6, Date: 17.09.2019). Written informed consent was obtained from all participants before enrollment. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patients and Data Collection

A total of 100 patients with acute pancreatitis were consecutively enrolled. The collected data included demographic characteristics, clinical parameters, laboratory measurements, and clinical outcomes. Peripheral blood samples were collected on days 1, 3, and 7 of hospitalization. Plasma was separated and stored at −80°C for subsequent biomarker analysis.

Diagnostic Criteria

The diagnosis of acute pancreatitis was established according to the Revised Atlanta Classification and required at least two of the following three criteria: (1) abdominal pain consistent with acute pancreatitis; (2) serum amylase and/or lipase levels ≥3 times the upper limit of normal; and (3) characteristic findings on contrast-enhanced computed tomography, magnetic resonance imaging, or ultrasonography.

Etiology of Acute Pancreatitis

Biliary stone disease was the predominant etiological factor and was identified in 83 patients (83%). A pancreatic cyst was detected in 6 patients (6%). In 11 patients (11%), no definitive etiological factor could be identified despite a comprehensive diagnostic workup; therefore, these cases were classified as idiopathic acute pancreatitis. No cases of hypertriglyceridemia-

induced or alcohol-induced pancreatitis were recorded in this cohort. The distribution of etiologies was similar between the plasmapheresis and conventional therapy groups (p=0.79).

Definitions

Clinical deterioration: A composite endpoint defined as in-hospital mortality or new or worsening organ failure requiring admission to the intensive care unit (ICU). Organ failure was defined as a Modified Marshall score ≥2 for any organ system.

- Improved subgroup: Patients in the conventional therapy group who had no organ failure, experienced an uncomplicated clinical course, and did not require ICU admission.
- Worsened subgroup: Patients in the conventional therapy group who developed new or persistent organ failure (Modified Marshall score ≥2), required ICU admission, or died.

Inclusion Criteria

The inclusion criteria were as follows: (1) age ≥18 years; (2) diagnosis of acute pancreatitis according to the Revised Atlanta Classification; and (3) admission within 7 days of symptom onset.

Exclusion Criteria

The exclusion criteria were as follows: (1) chronic pancreatitis; (2) pancreatic malignancy; (3) pregnancy; (4) transfer from another hospital more than 48 hours after admission; and (5) refusal to provide informed consent.

Study Groups and Treatment Allocation

All patients received standard guideline-recommended therapy.

Standard Conventional Therapy

All patients received standard guideline-recommended therapy for acute pancreatitis, including aggressive intravenous fluid resuscitation with crystalloids (Ringer's lactate or normal saline), early enteral nutrition through a nasogastric or nasoduodenal tube when oral intake was not tolerated, and analgesia as required. Patients with organ failure received supportive care in the ICU, including vasopressor support for hemodynamic instability, mechanical ventilation for respiratory failure, and renal replacement therapy for acute kidney injury when indicated. Antibiotics were administered only in cases of documented or suspected infected pancreatic necrosis. All therapeutic decisions were made by the treating clinical team in accordance with international guidelines for the management of acute pancreatitis.

The decision to administer adjunctive plasmapheresis was made by the treating physician based on clinical judgment regarding disease severity. Treatment allocation was nonrandomized. Patients were divided into two groups:

- Plasmapheresis group (n=68): Conventional therapy plus plasmapheresis.
- Conventional therapy group (n=32): Conventional therapy alone.

For the secondary analysis, the conventional therapy group was subdivided post hoc into:

- Worsened subgroup (n=17): Patients who met the definition of clinical deterioration.
- Improved subgroup (n=15): Patients who did not experience clinical deterioration.

Plasmapheresis Procedure

Plasmapheresis was performed using a centrifugal apheresis platform (Spectra Optia, Terumo BCT, Tokyo, Japan). Each session lasted 1–3 hours and used 5% human albumin as the replacement fluid at a volume equivalent to 1.0–1.5 times the patient's estimated plasma volume. Procedures were performed 2–3 times weekly based on the patient's clinical status.

Laboratory Investigations

Biomarker assessment: Peripheral blood samples were collected on days 1, 3, and 7 of hospitalization. Plasma was separated by centrifugation and stored at −80°C until analysis. Soluble E-selectin (sE-selectin) and von Willebrand factor (vWF) were measured using commercial enzyme-linked immunosorbent assay (ELISA) kits (Cloud-Clone Corp., Katy, TX, USA) according to the manufacturer's protocols. Vascular endothelial growth factor (VEGF) and endothelin-1 (ET-1) were measured using ELISA kits (R&D Systems, Minneapolis, MN, USA). All samples were analyzed in duplicate, and concentrations were determined using standard curves.

All biomarker assays were performed by laboratory personnel who were blinded to clinical outcomes and patient group allocation.

Clinical laboratory measurements: Serum amylase and lipase levels were measured at admission using standard automated laboratory methods. Organ failure was assessed daily during the first week of hospitalization using the Modified Marshall scoring system.

Statistical Analysis

Continuous variables were assessed for normality using the Shapiro–Wilk test and visual inspection of Q–Q plots. Normally distributed data were expressed as mean±standard deviation (SD) and compared using two-tailed independent-samples t tests for two-group comparisons or one-way analysis of variance (ANOVA) with post hoc tests for comparisons

Table 1. Baseline characteristics of patients with acute pancreatitis

Characteristic	All patients (n=100)	Plasmapheresis group (n=68)	Conventional therapy group (n=32)	p
Age, years	48.19±1.46	47.8±1.8	49.0±2.1	0.67
Sex, male/female	46/54	32/36	14/18	0.82
BMI, kg/m^2	28.57±0.44	28.3±0.5	29.1±0.7	0.34
BMI category, n, (%)				0.71
Underweight	1 (1)	1 (1.5)	0	
Normal weight (18.5–24.9)	17 (17)	12 (17.6)	5 (15.6)	
Overweight (25.0–29.9)	46 (46)	32 (47.1)	14 (43.8)	
Class I obesity (30.0–34.9)	32 (32)	20 (29.4)	12 (37.5)	
Class II obesity (35.0–39.9)	2 (2)	2 (2.9)	0	
Class III obesity (≥40.0)	2 (2)	1 (1.5)	1 (3.1)	
Comorbidities, n, (%)				
Diabetes mellitus	13 (13)	9 (13.2)	4 (12.5)	1.00
Hepatic steatosis	29 (29)	20 (29.4)	9 (28.1)	0.89
Arterial hypertension	12 (12)	8 (11.8)	4 (12.5)	1.00
Ischemic heart disease	9 (9)	6 (8.8)	3 (9.4)	1.00
COPD	4 (4)	3 (4.4)	1 (3.1)	1.00
Chronic kidney disease	4 (4)	3 (4.4)	1 (3.1)	1.00
Symptom duration at admission, n, (%)				0.45
≤5 days	27 (27)	20 (29.4)	7 (21.9)	
6–10 days	12 (12)	9 (13.2)	3 (9.4)	
≥11 days	61 (61)	39 (57.4)	22 (68.8)	

Data are presented as mean±standard error of the mean or number (%). p values compare the plasmapheresis and conventional therapy groups. BMI: Body mass index; COPD: Chronic obstructive pulmonary disease.

among multiple groups. Non-normally distributed data were expressed as median and interquartile range (IQR) and compared using the Mann–Whitney U test or Kruskal–Wallis test. Categorical variables were expressed as frequencies and percentages and compared using the chi-square test or Fisher's exact test, as appropriate.

Receiver operating characteristic (ROC) curve analysis was performed to assess the predictive ability of biomarkers for clinical deterioration. Areas under the curve (AUCs) with 95% confidence intervals (CIs) were calculated, and optimal cutoff values were determined using Youden's index.

To address potential confounding resulting from nonrandomized treatment allocation, multivariable logistic regression analysis was performed to assess the independent association between plasmapheresis and clinical deterioration. The model was adjusted for baseline covariates, including age, body mass index (BMI), and admission levels of VEGF, vWF, ET-1, and sE-selectin. The results are reported as adjusted odds ratios (ORs) with 95% CIs. A two-sided $p<0.05$ was considered statistically significant.

Biomarker trajectories over time were compared among the groups using repeated-measures ANOVA, with F statistics and degrees of freedom reported. Correlations between biomarker levels and clinical outcomes were assessed using Pearson or Spearman correlation coefficients, as appropriate, with 95% CIs reported for the primary correlations.

Survival analysis was performed using the Kaplan–Meier method, with patients censored at hospital discharge or at the end of the 30-day follow-up period. Survival curves were compared using the log-rank test, and median survival times with 95% CIs were reported.

No adjustment was made for multiple comparisons because these analyses were exploratory. Missing data were minimal (<5%) and were handled using complete-case analysis.

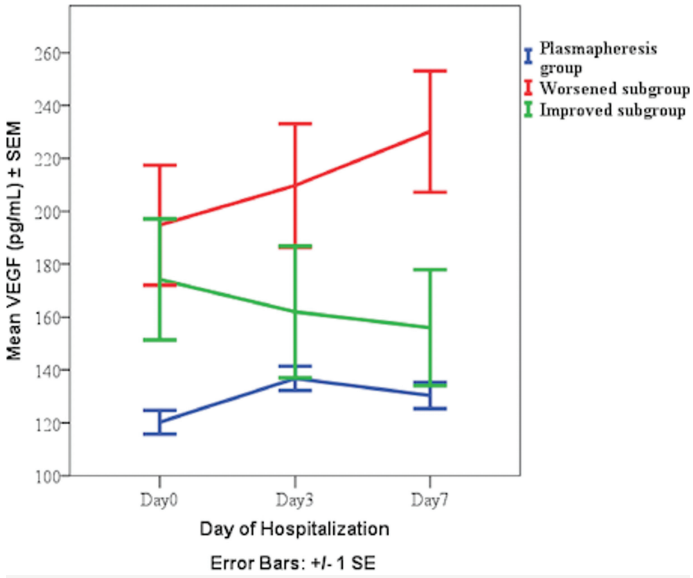

Figure 1. VEGF trajectories in patients with acute pancreatitis. Mean±SEM levels of vascular endothelial growth factor (VEGF) on days 1, 3, and 7 in the plasmapheresis group (n=68), Worsened subgroup (n=17), and Improved subgroup (n=15).

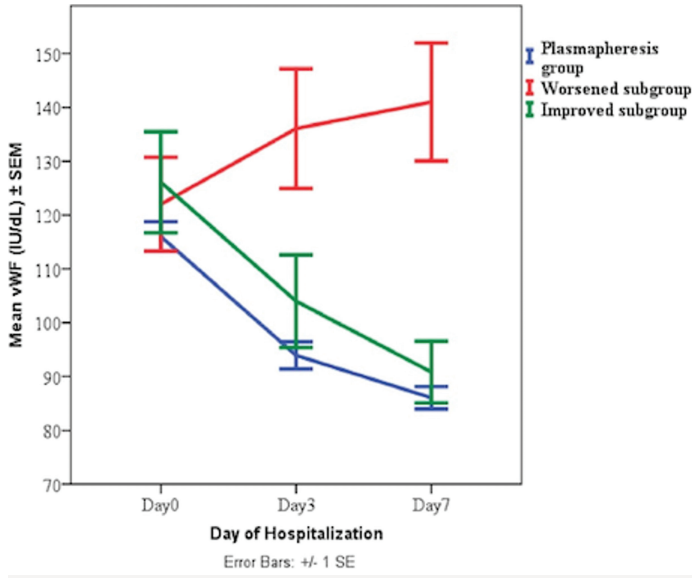

Figure 2. vWF trajectories in patients with acute pancreatitis. Mean±SEM levels of von Willebrand factor (vWF) on days 1, 3, and 7 in the plasmapheresis group (n=68), Worsened subgroup (n=17), and Improved subgroup (n=15).

Outliers were identified through boxplot inspection and retained in the analysis after verification. A two-sided $p<0.05$ was considered statistically significant.

All analyses were performed using IBM SPSS Statistics, version 22 (IBM Corp., Armonk, NY, USA).

RESULTS

Baseline Characteristics and Admission Biomarker Levels

Baseline characteristics are summarized in Table 1. The plasmapheresis and conventional therapy groups were comparable, although the conventional therapy group had higher admission levels of VEGF (185.14 vs. 120.20 pg/mL, $p<0.05$) and ET-1 ($p<0.001$). Within the conventional therapy group, the Worsened subgroup (n=17) had higher baseline levels of all biomarkers than the Improved subgroup (n=15), although the differences in VEGF and sE-selectin levels did not reach statistical significance.

Biomarker Trajectories

Serial biomarker measurements revealed distinct temporal patterns according to treatment group and clinical course.

VEGF: Repeated-measures ANOVA demonstrated significant differences in VEGF trajectories among the groups ($F=51.585$, $p<0.001$). The plasmapheresis group showed a progressive decline from day 1 to day 7. In contrast, the Worsened subgroup exhibited increasing VEGF levels over time, whereas the Improved subgroup showed a gradual decline (Fig. 1). Higher VEGF levels on days 3 and 7 were correlated with prolonged hospitalization and a longer ICU stay ($p<0.05$).

von Willebrand factor (vWF): vWF levels decreased over time in the plasmapheresis group but increased in the Worsened subgroup. By day 7, the mean vWF level was 86.04 IU/dL in the plasmapheresis group compared with 141.01 IU/dL in the Worsened subgroup ($p<0.001$) (Fig. 2). vWF showed a weak but significant association with the severity of organ failure.

Endothelin-1: ET-1 trajectories differed markedly among the groups throughout treatment ($F=952.966$, $p<0.001$). The plasmapheresis group demonstrated a rapid decline, whereas the Worsened subgroup maintained persistently elevated levels (Fig. 3). High ET-1 levels on days 3 and 7 were strongly associated with mortality ($r\approx-0.36$ to -0.48, $p<0.001$) and prolonged hospitalization.

Soluble E-selectin (sE-selectin): sE-selectin levels declined steadily in the plasmapheresis group but remained elevated in the Worsened subgroup ($p<0.001$) (Fig. 4). Higher sE-selectin levels on days 3 and 7 were correlated with longer hospitalization and a lower probability of survival ($p<0.001$) (Fig. 5).

Multivariable Analysis

To determine whether plasmapheresis remained independently associated with clinical deterioration after

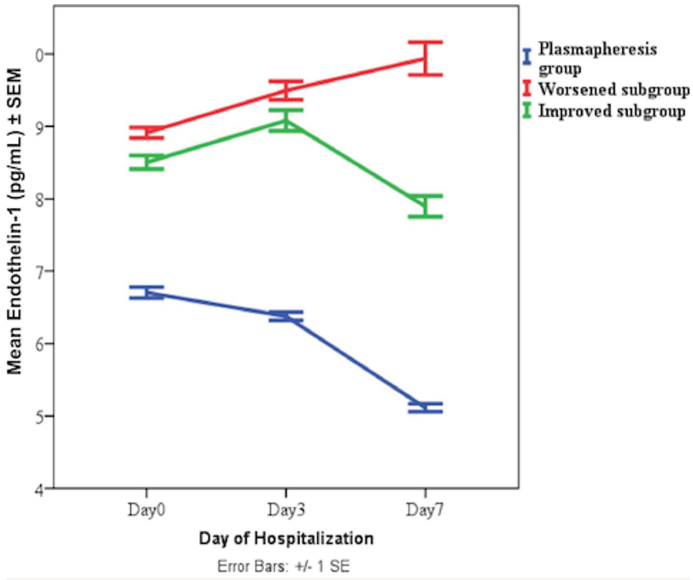

Figure 3. Endothelin-1 trajectories in patients with acute pancreatitis. Mean±SEM levels of endothelin-1 on days 1, 3, and 7 in the plasmapheresis group (n=68), Worsened subgroup (n=17), and Improved subgroup (n=15).

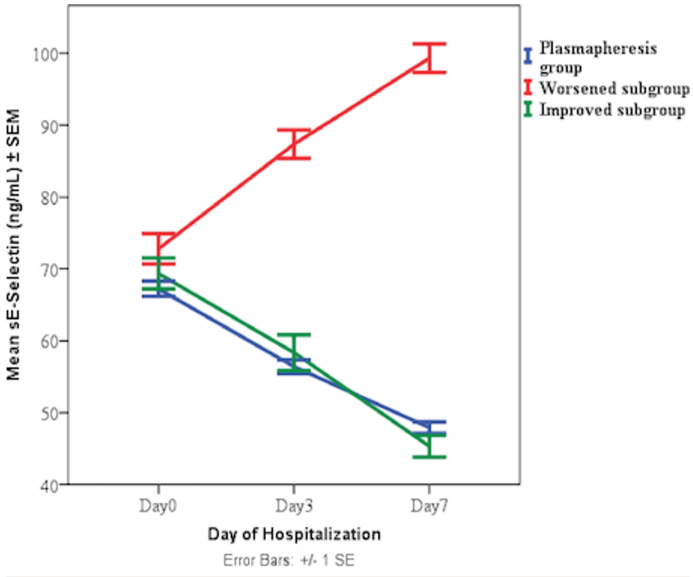

Figure 4. sE-selectin trajectories in patients with acute pancreatitis. Mean±SEM levels of soluble E-selectin (sE-selectin) on days 1, 3, and 7 in the plasmapheresis group (n=68), Worsened subgroup (n=17), and Improved subgroup (n=15).

adjustment for potential confounders, multivariable logistic regression analysis was performed. After adjustment for age, BMI, and admission levels of VEGF, vWF, ET-1, and sE-selectin, plasmapheresis remained independently

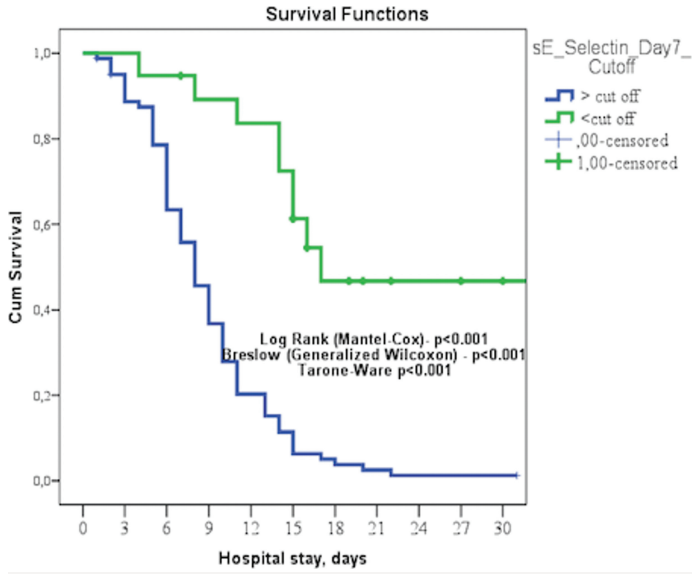

Figure 5. Kaplan–Meier survival curves for patients stratified according to the day 7 sE-selectin cutoff value of 59.5 ng/mL.

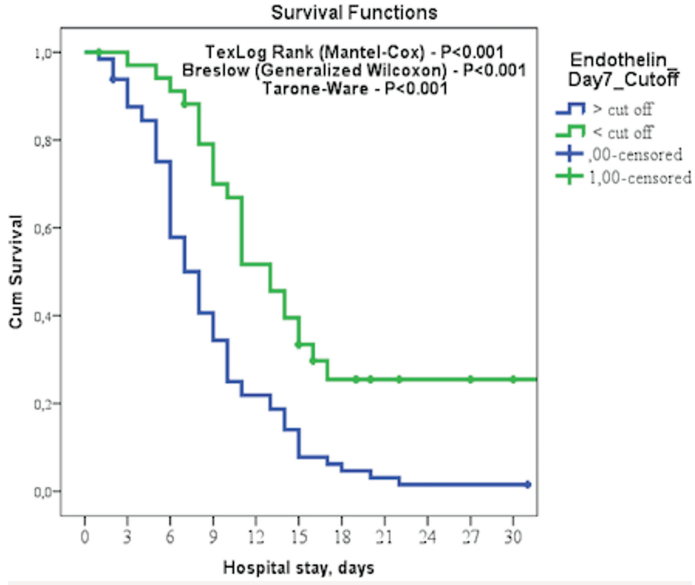

Figure 6. Kaplan–Meier survival curves for patients stratified according to the day 7 endothelin-1 cutoff value of 5.8 pg/mL.

associated with a lower rate of clinical deterioration (adjusted OR=0.21, 95% CI: 0.07–0.58, p=0.002). Among the biomarkers, admission sE-selectin (adjusted OR=1.82 per 10-ng/mL increase, 95% CI: 1.25–2.64, p=0.002) and ET-1 (adjusted OR=1.58 per 1-pg/mL increase, 95% CI: 1.12–2.22, p=0.009) were significant independent predictors of clinical deterioration.

Table 2. Predictive accuracy of endothelial dysfunction biomarkers measured on day 3 for clinical deterioration in acute pancreatitis

Biomarker	AUC	95% CI	Interpretation
VEGF	0.744 (p=0.005)	—	Good predictor
vWF	0.623 (p=0.153)	—	Weak predictor
Endothelin-1	0.771 (p=0.002)	—	Good predictor
sE-selectin	**0.905 (p<0.001)**	—	Excellent predictor

AUC: Area under the receiver operating characteristic curve; CI: Confidence interval; ICU: Intensive care unit; sE-selectin, soluble E-selectin; VEGF: Vascular endothelial growth factor; vWF: von Willebrand factor. Clinical deterioration was defined as a composite endpoint of in-hospital mortality or new or worsening organ failure requiring ICU admission.

Table 3. Predictive accuracy of endothelial dysfunction biomarkers measured on day 7 for clinical deterioration in acute pancreatitis

Biomarker	AUC	95% CI	Interpretation
VEGF	0.790 (p=0.001)	—	Good predictor
vWF	0.746 (p=0.004)	—	Moderate predictor
Endothelin-1	0.847 (p<0.001)	—	Very good predictor
sE-selectin	0.858 (p<0.001)	—	Excellent predictor

AUC: Area under the receiver operating characteristic curve; CI: Confidence interval; ICU: Intensive care unit; sE-selectin, soluble E-selectin; VEGF: Vascular endothelial growth factor; vWF: von Willebrand factor. Clinical deterioration was defined as a composite endpoint of in-hospital mortality or new or worsening organ failure requiring ICU admission.

Predictive Accuracy of Biomarkers

Receiver operating characteristic curve analysis demonstrated that endothelial biomarkers, particularly sE-selectin and ET-1, were strong predictors of clinical deterioration on both day 3 and day 7 (Tables 2 and 3). On day 3, sE-selectin demonstrated excellent predictive accuracy (AUC=0.905, p<0.001), followed by ET-1 (AUC=0.771, p=0.002) and VEGF (AUC=0.744, p=0.005). vWF was a weak predictor on day 3 (AUC=0.623, p=0.153), but its predictive accuracy improved by day 7 (AUC=0.746, p=0.004). The predictive accuracy of most biomarkers improved or remained stable over time. The optimal prognostic cutoff values derived using Youden's index are presented in Table 4.

Table 4. Optimal prognostic cutoff values for endothelial dysfunction biomarkers on days 3 and 7 of hospitalization

Biomarker	Cut-off value on day 3	Cut-off value on day 7
VEGF	102.5 pg/mL	113.7 pg/mL
vWF	85.7 IU/dL	105.3 IU/dL
Endothelin-1	6.9 pg/mL	5.8 pg/mL
sE-selectin	56.9 ng/mL	59.5 ng/mL

ROC: Receiver operating characteristic; sE-selectin, soluble E-selectin; VEGF: Vascular endothelial growth factor; vWF: von Willebrand factor. Optimal cutoff values were determined using Youden's index (J) from ROC analysis for the composite endpoint of clinical deterioration, defined as mortality or multiorgan dysfunction syndrome.

Survival Analysis

Kaplan–Meier analysis using all-cause mortality as the endpoint revealed clear stratification of outcomes according to ET-1 levels (Fig. 6). Patients with day 7 ET-1 levels <5.8 pg/mL had a survival rate of 96.9% and a median survival time of 30.5 days, compared with a survival rate of 68.6% and a median survival time of 22.7 days among those with ET-1 levels ≥5.8 pg/mL (log-rank p<0.001). Similar stratification was observed for sE-selectin (Fig. 5), with patients below the cutoff value of 59.5 ng/mL demonstrating significantly better survival than those above the cutoff (log-rank p<0.001). Cox proportional hazards regression was not performed because the primary aim of this analysis was to visually demonstrate risk stratification using the derived biomarker cutoff values.

DISCUSSION

This study demonstrates that serial endothelial dysfunction biomarkers are strong predictors of clinical deterioration in AP and that their trajectories differed among patients who received adjunctive plasmapheresis. TPE has been shown to improve hemodynamics and survival in sepsis.[12,13] These benefits have also been supported by systematic reviews.[14] Its use is increasingly supported in inflammatory crises, including pediatric sepsis and cytokine storm syndromes, highlighting its potential as an endothelial-stabilizing intervention.[15–17]

We acknowledge that established severity indices, such as the BISAP, APACHE II, CTSI, and SOFA scores, were not calculated in this study. Our primary objective was to evaluate whether a panel of endothelial biomarkers measurable from a single blood sample could provide a more streamlined and accessible approach to early risk stratification in AP while avoiding the complexity and resource requirements of multiparameter scoring systems. Although these established scores have proven value, they are often cumbersome to calculate in real time and require multiple laboratory and clinical parameters that may not be universally available. The absence of these scores limits our ability to fully characterize baseline severity and confirm comparability between the groups. However, baseline biomarker levels were comparable between the plasmapheresis and conventional therapy groups, and our multivariable analysis was adjusted for key baseline indicators, including age, BMI, and admission biomarker levels. Nevertheless, future studies incorporating established severity indices are needed to validate our findings and compare the prognostic performance of endothelial biomarkers with that of these standardized scoring systems.

We evaluated the association of plasmapheresis with clinical outcomes and endothelial dysfunction in patients with AP and compared the findings with those of patients receiving conventional guideline-based therapy. Previous research on plasmapheresis in AP has focused predominantly on hypertriglyceridemia-induced cases, with heterogeneous findings; some studies have reported clinical benefits, whereas others have demonstrated limited efficacy or procedure-related risks.[18–21] Our study differs in that most enrolled patients had biliary or idiopathic pancreatitis, and plasmapheresis was used primarily as a strategy to mitigate endothelial injury rather than rapidly reduce triglyceride levels.

Patients receiving plasmapheresis had more favorable outcomes. Among the 68 patients who received adjunctive therapy, the mortality rate was 1.47%, compared with 6.25% in the conventional therapy group. However, given the nonrandomized design, these differences should be interpreted as associations rather than causal effects. Notably, both deaths in the conventional therapy group occurred in the Worsened subgroup, which comprised patients whose clinical conditions deteriorated despite standard therapy, resulting in a subgroup-specific mortality rate of 11.76%. These findings suggest that early modulation of endothelial dysfunction may attenuate disease progression and reduce the likelihood of multiorgan involvement. Comparable improvements have been described in recent studies, in which plasmapheresis was associated with reductions in circulating inflammatory mediators, endothelial activation markers, and prothrombotic factors, thereby stabilizing microvascular function and accelerating clinical recovery.[9,12,13,16]

Our analysis revealed that the endothelial biomarkers VEGF, vWF, ET-1, and E-selectin were strongly associated with disease severity, organ dysfunction, length of hospitalization, and survival. vWF demonstrated comparatively weaker predictive performance, particularly on day 3 (AUC=0.623, p=0.153), although its accuracy improved by day 7 (AUC=0.746, p=0.004). This finding may be explained by the fact that vWF is an acute-phase reactant released not only from activated endothelial cells but also from platelets and megakaryocytes in response to systemic inflammation, stress, and tissue injury.[4,5] Consequently, vWF levels may be elevated in a broad range of conditions other than endothelial dysfunction, including acute inflammatory states and thrombotic events, which may reduce its specificity as a prognostic marker in AP. In contrast, sE-selectin and ET-1 are more specifically associated with endothelial activation and vascular permeability, which may account for their superior predictive accuracy.

Patients in the conventional therapy group, particularly those in the Worsened subgroup, demonstrated persistently elevated biomarker levels, whereas those who underwent plasmapheresis experienced significant reductions by days 3 and 7. These findings are consistent with previous studies highlighting the central roles of endothelial barrier disruption, microcirculatory thrombosis, and dysregulated angiogenesis in the pathophysiology of severe AP.

The dynamic behavior of biomarkers during treatment provides additional insight. Plasmapheresis was associated with early reductions in VEGF, ET-1, and E-selectin, which are molecules implicated in increased vascular permeability, vasoconstriction, and leukocyte adhesion. Meanwhile, vWF, a marker of endothelial damage and platelet activation, declined more slowly but still showed a downward trend with plasmapheresis. In contrast, patients with clinical deterioration demonstrated increasing levels of these markers, consistent with progressive endothelial injury and microvascular failure. Taken together, our results support the view that endothelial dysfunction is not merely a consequence of AP but may also be a driver of clinical deterioration.

Overall, the findings indicate that plasmapheresis may mitigate the endothelial component of AP pathophysiology, thereby reducing complications and improving outcomes. This interpretation is consistent with growing evidence suggesting that targeting endothelial stabilization through extracorporeal blood purification or pharmacologic interventions may represent a promising adjunctive therapeutic strategy for severe forms of the disease.

Strengths and Limitations

Strengths

The prospective study design, with serial measurements obtained on days 1, 3, and 7, allowed a detailed evaluation of biomarker dynamics.

The comprehensive endothelial biomarker panel, including VEGF, vWF, ET-1, and E-selectin, provided a mechanistic perspective beyond that offered by classical inflammatory markers.

The inclusion of clinical outcomes, such as organ failure, ICU stay, and mortality, enabled a meaningful assessment of prognostic performance.

The use of multimodal statistical approaches, including ROC curve analysis and repeated-measures ANOVA, ensured a robust interpretation of biomarker significance.

The novel application of plasmapheresis in biliary and non-hypertriglyceridemic pancreatitis adds original value to the existing literature.

Limitations

Several limitations of this study should be acknowledged. First, allocation to plasmapheresis was nonrandomized and based on clinical discretion, introducing a substantial risk of selection bias and confounding by indication. Although multivariable adjustment was performed for baseline severity indicators, unmeasured confounding cannot be entirely excluded. Therefore, all observed associations between plasmapheresis and clinical outcomes should be interpreted as associative rather than causal.

Second, the single-center design limits the generalizability of our findings to broader populations and different healthcare settings. External validation in multicenter cohorts is necessary before the proposed biomarker cutoff values can be adopted in clinical practice.

Third, although the sample size was adequate for the primary analyses, it may have been insufficient to detect subtle subgroup differences or permit robust derivation of cutoff values. The post hoc subdivision of the conventional therapy cohort further limits comparability among the groups.

Fourth, the absence of long-term follow-up limited the evaluation of delayed complications and recurrent pancreatitis.

Fifth, biomarker assays were performed using kits from a single manufacturer, which may limit comparability across studies, although internal consistency was strong.

Accordingly, all observed associations between plasmapheresis and clinical outcomes should be interpreted as associative rather than causal, and no therapeutic claims can be made based on these data. Randomized controlled trials are needed to determine whether plasmapheresis has a causal protective effect.

Furthermore, established severity indices, such as the BISAP, APACHE II, CTSI, and SOFA scores, were not calculated, limiting our ability to fully characterize baseline disease severity and confirm group comparability beyond the measured biomarkers. This limitation should be addressed in future validation studies.

Additionally, Cox proportional hazards regression was not performed to estimate adjusted hazard ratios for mortality. Although our Kaplan–Meier analysis visually demonstrated the prognostic value of biomarker cutoff values, future studies should incorporate Cox regression to provide adjusted effect estimates and account for potential confounders.

Finally, the exploratory nature of the analyses, involving multiple comparisons across several biomarkers and time points, increased the risk of type I error. Accordingly, our findings should be considered hypothesis-generating and require confirmation in prospective, randomized, and adequately powered trials.

CONCLUSION

Serial endothelial dysfunction biomarkers, particularly sE-selectin and ET-1, are strong early predictors of clinical deterioration in acute pancreatitis. Plasmapheresis was associated with favorable biomarker trajectories and significantly lower rates of clinical deterioration than those observed in the Worsened subgroup of patients receiving conventional therapy alone. These findings support the role of endothelial biomarkers in early risk stratification and suggest that endothelial dysfunction may represent a modifiable therapeutic target. Randomized controlled trials are needed to confirm these associations and establish the efficacy of biomarker-guided plasmapheresis in acute pancreatitis.

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REFERENCES

1. Krauß LU, Brosig AM, Schlosser S, Pavel V, Mehrl A, Gülow K, et al. Therapeutic Plasma Exchange in ICU Patients with Acute Hypertriglyceridemia-Induced Pancreatitis Improves Patient Outcomes. Dig Dis 2023;41(4):647-55. [CrossRef]
2. Zheng C, Zheng Y, Zheng Z. Therapeutic plasma exchange decreases serum triglyceride level rapidly and reduces early recurrence rate but no advantages in improving outcomes for patients with hyperlipidemic acute pancreatitis: a retrospective propensity score matching

analysis based on twenty year's experience. BMC Endocr Disord 2024;24(1):32. [CrossRef]

3. Stahl K, Schmidt JJ, Seeliger B, Schmidt BMW, Welte T, Haller H, et al. Effect of therapeutic plasma exchange on endothelial activation and coagulation-related parameters in septic shock. Crit Care 2020;24(1):71. [CrossRef]
4. Stahl K, Hillebrand UC, Kiyan Y, Seeliger B, Schmidt JJ, Schenk H, et al. Effects of therapeutic plasma exchange on the endothelial glycocalyx in septic shock. Intensive Care Med Exp 2021;9(1):57. [CrossRef]
5. Knaup H, Stahl K, Schmidt BMW, Idowu TO, Busch M, Wiesner O, et al. Early therapeutic plasma exchange in septic shock: a prospective open-label nonrandomized pilot study focusing on safety, hemodynamics, vascular barrier function, and biologic markers. Crit Care 2018;22(1):285. [CrossRef]
6. Cibor D, Owczarek D, Butenas S, Salapa K, Mach T, Undas A. Levels and activities of von Willebrand factor and metalloproteinase with thrombospondin type-1 motif, number 13 in inflammatory bowel diseases. World J Gastroenterol 2017;23(26):4796-805. [CrossRef]
7. Takaya H, Namisaki T, Kitade M, Kaji K, Nakanishi K, Tsuji Y, et al. VWF/ADAMTS13 ratio as a potential biomarker for early detection of hepatocellular carcinoma. BMC Gastroenterol. 2019;19(1):167. [CrossRef]
8. Kuklin V, Sovershaev M, Bjerner J, Keith P, Scott LK, Thomas OMT, et al. Influence of therapeutic plasma exchange treatment on short-term mortality of critically ill adult patients with sepsis-induced organ dysfunction: a systematic review and meta-analysis. Crit Care 2024;28(1):12. [CrossRef]
9. Kielstein JT. Hemoperfusion and plasmapheresis in the intensive care unit: A bridge over troubled water?. Wien Klin Mag 2023:1-6. German. [CrossRef]
10. Stahl K, Wand P, Seeliger B, Wendel-Garcia PD, Schmidt JJ, Schmidt BMW, et al. Clinical and biochemical endpoints and predictors of response to plasma exchange in septic shock: results from a randomized controlled trial. Crit Care 2022;26(1):134. [CrossRef]
11. David S, Bode C, Stahl K; EXCHANGE-2 Study group. EXCHANGE-2: investigating the efficacy of add-on plasma exchange as an adjunctive strategy against septic shock-a study protocol for a randomized, prospective, multicenter, open-label, controlled, parallel-group trial. Trials 2023;24(1):277. [CrossRef]
12. Ahmed RM, Soliman AR, Yousry A, Marzouk K, Faris F. Efficacy of 4-hour rescue therapeutic plasma exchange in severe septic shock patients. Rom J Intern Med 2020;58(2):75-80. [CrossRef]
13. Keith PD, Wells AH, Hodges J, Fast SH, Adams A, Scott LK. The therapeutic efficacy of adjunct therapeutic plasma exchange for septic shock with multiple organ failure: a single-center experience. Crit Care 2020;24(1):518. [CrossRef]
14. Hernandez GN, Francis AJ, Hamid P. Enhancing Survival in Septic Shock: A Systematic Review and Meta-Analysis of the Efficacy of Plasma Exchange Therapy. Cureus 2024;16(5):e60947. [CrossRef]
15. Stahl K, Bode C, Seeliger B, Wendel-Garcia PD, David S. Current clinical practice in using adjunctive extracorporeal blood purification in sepsis and septic shock: results from the ESICM "EXPLORATION" survey. Intensive Care Med Exp 2024;12(1):5. [CrossRef]
16. Okajima K, Hayakawa I, Tsuboi N, Shimura K, Ishiguro A, Abe Y. Early therapeutic plasma exchange may lead to complete neurological recovery in moderate to severe influenza-associated acute necrotizing encephalopathy. Brain Dev 2022;44(7):492-7. [CrossRef]
17. Aygün F, Varol F, Durak C, Talip Petmezci M, Kacar A, Dursun H, et al. Evaluation of Continuous Renal Replacement Therapy and Therapeutic Plasma Exchange, in Severe Sepsis or Septic Shock in Critically Ill Children. Medicina (Kaunas) 2019;55(7):350. [CrossRef]
18. Samarasinghe S, Avari P, Meeran K, Cegla J. Management of hypertriglyceridaemic pancreatitis in the acute setting and review of literature. BMJ Case Rep 2018;11(1):e227594. [CrossRef]
19. Uyar S, Harmandar F, Kök M, Taş Z, Dolu S, Tokuç A, et al. Management of hypertriglyceridemia induced acute pancreatitis and therapeutic plasmapheresis : Report of nine cases and review of literature. Acta Gastroenterol Belg 2017;80(1):71-4.
20. Liu R, Lu J, Zhang D, Lu W, Yu Z, Shao X, et al. Timely Application of Plasma Exchange to Correct Acute Pancreatitis Related to Serum Triglyceride Levels: A Report of 6 Cases and a Literature Review. Am J Case Rep 2024;25:e944763. [CrossRef]
21. Chen Z, Huang X, Han N, Guo Y, Chen J, Ning Y, et al. Total cholesterol concentration predicts the effect of plasmapheresis on hypertriglyceridemic acute pancreatitis: a retrospective case-control study. BMC Gastroenterol 2021;21(1):3. [CrossRef]