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TIME-STRATIFIED PROGNOSTIC VALUE OF ENDOTHELIAL BIOMARKERS IN ACUTE PANCREATITIS, WITH SOLUBLE E-SELECTIN AS AN EARLY MORTALITY PREDICTOR AND VON WILLEBRAND FACTOR AS A PREDICTOR OF ORGAN FAILURE

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Endothelial dysfunction contributes to severity in acute pancreatitis. Endothelial biomarkers were measured serially on days 1, 3, and 7 in 100 patients with acute pancreatitis. Biomarker patterns differed by clinical outcome and sampling time. In patients with worsened outcome, sE-selectin levels were highest on day 3 (87.35±1.97 ng/mL vs. 58.35±2.49 ng/mL in improved outcome), while von Willebrand factor levels showed divergence on day 7 (141.01±10.96 U/dL vs. 90.85±5.73 U/dL). ROC analysis suggested that day 3 sE-selectin ≥56.9 ng/mL might identify patients at risk for mortality (AUC 0.905; sensitivity 92.3 %, specificity 83.9 %), while day 7 von Willebrand factor ≥105 U/dL showed potential for identifying multiorgan dysfunction risk (AUC 0.746 (95 % CI: 0.596–0.896). sE-selectin elevations corresponded with early clinical worsening, while persistent von Willebrand factor elevation was associated with late organ dysfunction. These preliminary findings support further investigation of time-stratified biomarker assessment in larger, independent cohorts.

Key words: acute pancreatitis, endothelial dysfunction, biomarkers, sE-Selectin, von Willebrand factor

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ЧАСОВА СТРАТИФІКАЦІЯ ПРОГНОСТИЧНОЇ ЗНАЧУЩОСТІ РОЗЧИННОГО Е-СЕЛЕКТИНУ ЯК РАННЬОГО ПРЕДИКТОРА ЛЕТАЛЬНОСТІ ТА ФАКТОРА ВІЛЛЕБРАНДА ЯК ПРЕДИКТОРА ОРГАННОЇ НЕДОСТАТНОСТІ ПРИ ГОСТРОМУ ПАНКРЕАТИТІ

Ендотеліальна дисфункція впливає на тяжкість перебігу гострого панкреатиту. Біомаркери ендотелію вимірювали послідовно на 1-й, 3-й та 7-й дні у 100 пацієнтів із гострим панкреатитом. Показники біомаркерів відрізнялися залежно від клінічних результатів і часу відбору зразків. У пацієнтів із несприятливим результатом рівень sE-селектину був найвищим на 3-й день (87,35±1,97 нг/мл проти 58,35±2,49 нг/мл при сприятливому результаті), тоді як рівень фактора Віллебранда відрізнявся на 7-й день (141,01±10,96 од/дл проти 90,85±5,73 од/дл). ROC-аналіз показав, що рівень sE-селектину на 3-й день лікування ≥56,9 нг/мл може вказувати на пацієнтів із ризиком летального результату (AUC 0,905; чутливість 92,3 %, специфічність 83,9 %), тоді як на 7-й день фактор Віллебранда ≥105 од/дл продемонстрував потенціал для виявлення ризику поліорганної дисфункції (AUC 0,746 (95 % ДІ: 0,596–0,896). Підвищення рівня sE-селектину відповідало ранньому клінічному погіршенню, тоді як стійке підвищення рівня фактора Віллебранда було пов'язане з пізньою органною дисфункцією. Ці попередні дані підтверджують необхідність подальшого вивчення стратифікованої за часом оцінки біомаркерів у більших незалежних групах.

Ключові слова: гострий панкреатит, ендотеліальна дисфункція, біомаркери, sE-селектин, фактор Віллебранда.

Acute pancreatitis (AP) is a common gastrointestinal emergency with a highly variable clinical course [6, 13]. The endothelial dysfunction plays a central mechanism in the pathogenesis of the AP complications. The degradation of the endothelial glycocalyx has been directly linked to the subsequent development of multiple organ dysfunction (MOD) [1, 4].

Most investigations have measured the biomarkers of endothelial dysfunction at a single, time point, treating them as static "snapshots" of a dynamic process [7, 14].

Consequently, there is an unmet need for a time-stratified prognostic model that aligns with these distinct pathophysiological phases. We hypothesize that endothelial dysfunction markers reflect different aspects of this temporal evolution. Specifically, soluble E-selectin (sE-selectin), as a marker of acute leukocyte-endothelial interaction, may be most informative as an early warning signal for imminent clinical deterioration. Conversely, von Willebrand factor (vWF), reflecting sustained endothelial injury and pro-thrombotic alteration [2], may be a more powerful predictor of MOD.

The purpose of the study was to investigate the time-dependent patterns of soluble E-selectin and von Willebrand factor through serial measurements on days 1, 3, and 7 in a prospective cohort of patients with acute pancreatitis.

Materials and methods. This prospective cohort investigation was carried out at the Academic M.A. Topchubashov Scientific Surgery Center in Baku, Azerbaijan, from January 2019 through December 2022. The study enrolled 100 patients with acute pancreatitis.

Ethical Approval. The institutional ethics committee granted approval (Protocol No. 6, September 17, 2019), and all participants provided written informed consent prior to enrolment.

Exclusion Criteria**.** Patients were excluded if they met any of the following: age below 18 years;

confirmed pregnancy or lactation; pre-existing advanced chronic liver disease (Child-Pugh class B or C) or chronic kidney disease (stage 4-5); active malignancy; documented significant cardiovascular or hematologic disorders.

All participants received standard supportive care in accordance with international guidelines. Patients were allocated two management pathways: (1) Intervention Arm (n=68): Received standard therapy supplemented with plasmapheresis, intended to mitigate endothelial dysfunction; (2) Conventional Arm (n=32): Received standard therapy alone. The decision to employ plasmapheresis was non-randomized and influenced by factors including physician preference, clinical severity at presentation, and resource availability.

Post-hoc Clinical Categorization**.** Within the Conventional Arm, patients were retrospectively classified according to their actual clinical trajectory: Category A (Deteriorating Course, n=17) – patients who experienced in-hospital mortality or developed MOD; Category B (Uncomplicated Course, n=15) – patients who responded favourably to treatment, exhibiting mild disease without MOD.

Plasmapheresis was performed using standard centrifugal plasmapheresis system. Each session lasted 1-3 hours, processing 1–1.5 times the estimated plasma volume, with 5 % human albumin as replacement fluid. Patients typically received 2-3 sessions during the initial hospitalization week, at the attending physician's discretion.

Blood samples were obtained at three standardized time points: upon hospital arrival (Day 0), and subsequently on Day 3 and Day 7 of admission. Specimens were collected in citrate-containing tubes, centrifuged at 3,000 rpm for 15 minutes within two hours of collection, and plasma aliquots were stored at -80°C until analysis without freeze-thaw cycles.

Concentrations of sE-selectin and vWF were determined using commercial enzyme-linked immunosorbent assay kits following manufacturers' protocols. All measurements were performed in duplicate, with mean values used for analysis.

sE-Selectin: Human SELE/Soluble E-Selectin ELISA Kit (Cloud-Clone Corp., Katy, TX, USA; Catalog # SEA029Hu). Detection range: 39-2,500 pg/mL; sensitivity: <17 pg/mL. Intra-assay and inter-assay coefficients of variation were <10 % and <12 %, respectively.

vWF: Human vWF/Von Willebrand Factor ELISA Kit (Cloud-Clone Corp., Katy, TX, USA; Catalog # SEB696Hu). Detection range: 15.6-1,000 pg/mL; sensitivity: <5.8 pg/mL. Intra-assay and inter-assay CVs were <8 % and <10 %, respectively.

Assay procedure briefly: standards and samples were added to antibody-precoated 96-well plates. Following incubation and washing, biotin-conjugated detection antibody was added, followed by horseradish peroxidase-conjugated avidin. Tetramethylbenzidine substrate enabled color development, terminated by acid solution. Optical density was measured at 450 nm using a microplate reader (BioTek® ELx800). Standard curves were generated using four-parameter logistic fitting, and sample concentrations derived by interpolation.

Statistical Approach**.** Analyses employed IBM SPSS Statistics version 22 (IBM Corp., Armonk, NY, USA). Continuous data are presented as mean ± standard error of the mean (SEM) for normally distributed variables, or median with interquartile range (IQR) for non-normal distributions. Categorical data are shown as frequencies and percentages. Between-group comparisons utilized Student's t-test or Mann-Whitney U test for continuous variables, and Chi-square or Fisher's exact test for categorical variables, as appropriate. For multi-group comparisons, one-way ANOVA with post-hoc Tukey HSD was applied.

Relationships between biomarker concentrations and clinical outcomes (mortality, MOD, hospital stay) were examined using Pearson or Spearman correlation coefficients, as appropriate. Correlation coefficients (r) are presented with 95 % confidence intervals. Receiver operating characteristic curve analysis evaluated the capacity of sE-selectin and vWF at each time point to predict mortality and MOD. Area under the curve values is reported with 95 % confidence intervals. Optimal cut-off values were identified by maximizing Youden's index.

Results of the study. The mean age was 48.2±1.5 years, and the cohort included 46 (46 %) males and 54 (54 %) females. Serial measurements of soluble E-selectin (sE-selectin) revealed distinct temporal patterns across the three clinical groups. Notably, the Deteriorating Course group (Category A) exhibited consistently lower sE-selectin levels compared to the Uncomplicated Course group (Category B) and the overall cohort, with the most pronounced divergence observed on day 7. In contrast, patients with an uncomplicated course showed a progressive increase in sE-selectin concentrations over time, suggesting a potential protective or recovery-associated endothelial response. Serial sE-Selectin levels by clinical course were shown in Fig. 1.

In the Intervention Group (n=68), sE-selectin levels declined progressively from Day 0 (67.2±1.1 ng/mL) to Day 3 (56.4±0.9 ng/mL) and Day 7 (47.9±0.8 ng/mL). Within the Conventional Group, Category B showed a similar declining trend, with levels decreasing from 69.4±2.2 ng/mL on Day 0 to 58.4±2.5 ng/mL on Day 3 and 45.3±1.5 ng/mL on Day 7. In contrast, Category A exhibited persistently elevated sE-selectin levels throughout hospitalization: 72.8±2.1 ng/mL on Day 0, 87.4±2.0 ng/mL on Day 3, and 99.3±2.0 ng/mL on Day 7.

Two-way repeated measures ANOVA demonstrated a significant time-by-group interaction for sE-selectin levels (P=0.008), with a large effect size (partial η^2=0.511), confirming that the trajectory of sE-selectin over time differed significantly between groups.

Temporal Dynamics of vWF. Analysis of vWF revealed significant changes over time and between clinical groups. As early as day 0, patients in the Deteriorating Course group (Category A) already

exhibited higher von Willebrand factor levels compared to those with an Uncomplicated Course (Category B), with the difference becoming more pronounced by day 7 ($p<0.05$ for all time points, ANOVA with post-hoc). The Intervention group as a whole showed intermediate values, underscoring the close association between rising vWF concentrations and adverse clinical outcomes. Serial vWF levels by clinical course were shown on Fig. 2.

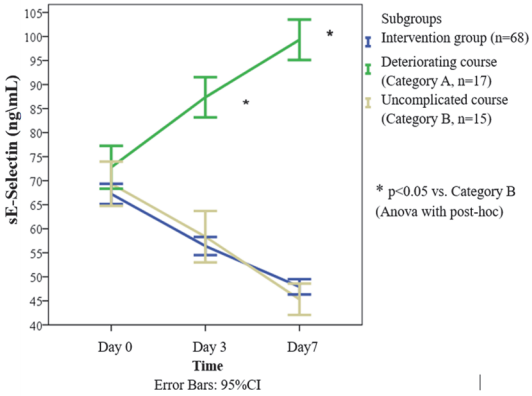

Fig. 1. Serial sE-Selectin levels by clinical course (Mean ± 95 % CI).

Note: Data are presented as mean with 95 % confidence intervals.

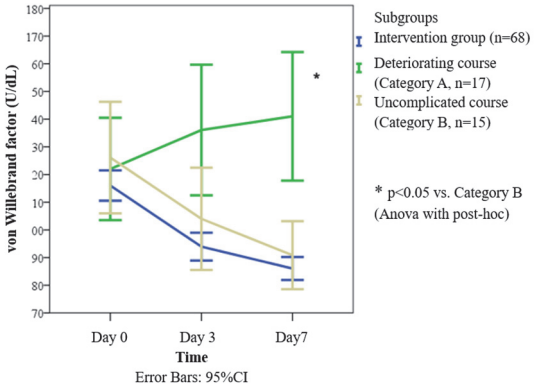

Fig. 2. Serial von Willebrand factor levels by clinical course (Mean ± 95 % CI).

Note: Data are presented as mean with 95 % confidence intervals.

A Linear Contrast test demonstrated a statistically significant overall change in vWF levels throughout hospitalization ($F=14.18$; $P<0.001$). While no significant differences were observed on Day 0, a clear divergence emerged by Day 3. The mean vWF level was 93.9±2.5 U/dL in the Intervention Group, compared to 136.1±11.1 U/dL in Category A and 104.0±8.6 U/dL in Category B of the Conventional Group. This pattern intensified by Day 7. Whereas vWF levels decreased in the Intervention Group (86.0±2.1 U/dL) and Category B (90.9±5.7 U/dL), they remained markedly elevated in Category A (141.0±11.0 U/dL). Post-hoc analyses (Tukey HSD) confirmed that Day 7 vWF levels in Category A were significantly higher than in all other groups ($P<0.001$ for all comparisons).

Association of sE-Selectin with Mortality**.** sE-selectin levels showed strong associations with patient survival. A statistically significant negative correlation was found between Day 3 sE-selectin and survival ($P<0.001$). This relationship was even stronger by Day 7 (Pearson r= -0.60; 95 % CI: -0.72 to -0.44; $P<0.001$; Spearman r= -0.42; 95 % CI: -0.58 to -0.23; $p<0.001$). sE-selectin levels were also positively correlated with the length of hospital stay (Day 3: Pearson r=0.49; 95 % CI: 0.33–0.63; $P<0.001$).

Prognostic Performance of sE-Selectin for Mortality**.** Receiver operating characteristic (ROC) curve analysis was performed on the Conventional Group (n=32) to evaluate the prognostic value of sE-selectin for predicting in-hospital mortality. On Day 3, sE-selectin demonstrated excellent predictive value with an area under the curve (AUC) of 0.905 (95 % CI: 0.836–0.975; $p<0.001$). The optimal cut-off value, determined by maximizing Youden's index, was 56.9 ng/mL, providing a sensitivity of 92.3 % (95 % CI: 64.0–99.8 %) and specificity of 83.9 % (95 % CI: 66.3–94.5 %) (Table 1).

Table 1

Optimal Prognostic Cut-off Values for Biomarkers with 95 % CI

Biomarker	Day	Cut-off Value	AUC (95 % CI)	P-value	Sensitivity % (95 % CI)	Specificity % (95 % CI)	Predicts
vWF	3	85.7 U/dL	0.623 (0.491–0.755)	>0.05	76.9 (46.2–95.0)	63.2 (46.0–78.2)	–
vWF	7	105 U/dL	0.746 (0.596–0.896)	<0.01	53.8 (25.1–80.8)	83.9 (74.5–91.0)	MOD
sE-Selectin	3	56.9 ng/mL	0.905 (0.844–0.966)	<0.001	92.3 (64.0–99.8)	83.9 (66.3–94.5)	Mortality
sE-Selectin	7	59.5 ng/mL	0.858 (0.783–0.933)	<0.001	85.0 (62.1–96.8)	81.3 (63.6–92.8)	Mortality

Note. vWF – von Willebrand factor; MOD – Multiple Organ Dysfunction; AUC – Area Under Curve; CI – Confidence Interval; $P<0.05$ indicated statistical significance.

On Day 7, sE-selectin maintained strong predictive value with an AUC of 0.858 (95 % CI: 0.731–0.984; $P<0.001$). The optimal cut-off value was 59.5 ng/mL, yielding a sensitivity of 85.0 % (95 % CI: 62.1–96.8 %) and specificity of 81.3 % (95 % CI: 63.6–92.8 %).

Survival Analysis**.** Kaplan-Meier survival analysis was performed to compare 30-day survival between patients stratified by the optimal sE-selectin cut-off values. For Day 3 sE-selectin, patients with levels ≥56.9 ng/mL (high-risk group, n=27) had significantly lower survival compared to those with levels <56.9 ng/mL (low-risk group, n=5) (log-rank $p=0.002$). All mortality events occurred in patients with sE-selectin above the cut-off.

For Day 7 sE-selectin, patients with levels ≥59.5 ng/mL (high-risk group, n=18) had significantly lower survival compared to those with levels <59.5 ng/mL (low-risk group, n=14) (log-rank $p<0.001$). The separation between survival curves was more pronounced at Day 7, with 55.6 % of patients in the high-risk group censored (alive at 30 days) compared to 0 % in the low-risk group.

Prognostic Performance of von Willebrand Factor for MOD**.** ROC analysis revealed that Day 7 vWF predicted MOD with an AUC of 0.746 (95 % CI: 0.596–0.896; P=0.004). The optimal cut-off value was 105 U/dL, providing a sensitivity of 53.8 % (95 % CI: 25.1–80.8 %) and specificity of 83.9 % (95 % CI: 74.5–91.0 %). In contrast, Day 3 vWF was not a significant predictor of MOD (AUC=0.735; 95 % CI: 0.457–1.000; P=0.257). Notably, the analysis of MOD was limited by the small number of events (n=2) in the Conventional Group, and these findings should be interpreted with caution. vWF levels were positively correlated with the length of hospital stay ($p<0.05$), indicating that higher vWF levels were associated with a longer recovery period.

This prospective cohort study investigated the temporal dynamics of endothelial biomarkers in acute pancreatitis and revealed several important findings. These findings suggest that sE-selectin may serve as an early warning signal reflecting acute leukocyte-endothelial interaction during the hyper-inflammatory phase, while persistent vWF elevation may indicate ongoing endothelial injury and pro-thrombotic alterations associated with late organ failure. Importantly, the prognostic value of both biomarkers was time-dependent, with optimal prediction windows differing by three to four days.

Discussion. Strengths and Limitations. Strengths. The primary strength of this study lies in its prospective design with serial biomarker measurements at three standardized time points (Days 0, 3, and 7). This approach allowed us to capture the dynamic evolution of endothelial dysfunction rather than relying on a single "snapshot," which has been a major limitation of previous investigations [7, 14]. The inclusion of both an intervention group (plasmapheresis) and a conventional therapy group enabled us to restrict the primary prognostic analysis to untreated patients, thereby avoiding confounding by treatment effects and providing unbiased estimates of natural biomarker behavior.

Additional strengths include the use of commercially available ELISA kits with low coefficients of variation, rigorous laboratory protocols with standardized sample processing and storage, and adherence to STROBE guidelines for reporting observational studies. The statistical approach included appropriate longitudinal analyses (two-way repeated measures ANOVA) with effect size estimation, correlation analyses with confidence intervals, and ROC curve analysis with Youden's index optimization and bootstrap validation.

Second, the single-center design may limit generalizability to other populations and settings. While our patient characteristics and outcomes are consistent with larger epidemiological studies [4, 8, 13], multicenter validation is essential before clinical implementation. Third, the post-hoc classification of patients into worsened and improved subgroups, while necessary for the analysis, introduces the risk of classification bias and overfitting. The optimal cut-off values derived from this dataset require prospective validation in independent cohorts.

Finally, as with all observational studies, residual confounding cannot be excluded. Although we adjusted for key covariates, unmeasured factors such as genetic polymorphisms, nutritional status, or variations in supportive care may have influenced the results.

Our finding that vWF levels, particularly on Day 7, are associated with adverse outcomes aligns with a growing body of evidence implicating endothelial injury in AP pathogenesis. Reuken et al. [2] studied 106 AP patients and reported that vWF, along with soluble CD206, identified patients at risk for severe or necrotizing pancreatitis, with an AUC of 0.81 for vWF alone. Similarly, Ida et al. [12] found that vWF levels correlated with disease severity and pancreatic necrosis in 57 AP patients. More recently, Sairam et al. [9] demonstrated that imbalance in the vWF-ADAMTS13 axis exists early in AP and predicts persistent organ failure, with an AUC of 0.84 for the vWF/ADAMTS13 ratio.

The temporal pattern observed in our study – with vWF elevation persisting through Day 7 in patients with MOD – echoes the findings, which reported that vWF antigen remained persistently high in non-survivors while gradually decreasing in survivors. They also identified an inverse correlation between vWF and ADAMTS13 activity, suggesting that impaired cleavage of ultra-large vWF multimers contributes to microvascular thrombosis and organ failure. They recently confirmed that vWF antigen independently predicted survival outcome (OR = 7.44, 95 % CI: 1.24–44.82) in 240 AP patients, and when combined with the TyG index achieved an AUC of 0.909 for prognosis prediction.

Our study extends these observations by demonstrating that the prognostic value of vWF is time-dependent, with optimal predictive performance for MOD occurring later in the disease course (Day 7) rather than at admission. This temporal specificity has not been previously reported and may have implications for the timing of therapeutic interventions targeting endothelial stabilization.

The role of E-selectin in AP has received less attention than vWF, but our findings suggest it may be equally important, particularly as an early marker. Nakajima et al. [9] demonstrated that E-selectin expression on activated endothelium is critical for leukocyte recruitment and transmigration, processes central to early inflammatory tissue damage. Walter et al. [15] showed that endothelial barrier dysfunction in experimental AP involves adhesion molecule upregulation, including E-selectin.

Clinically, our observation that Day 3 sE-selectin strongly predicts mortality (AUC 0.905) represents a novel finding. While earlier studies have reported elevated E-selectin in severe AP [12], no one have systematically examined its time-dependent prognostic value. The peak at Day 3 followed by decline in survivors, contrasted with persistent elevation in non-survivors, suggests that sE-selectin may reflect the intensity and duration of the initial endothelial activation response.

The observation that sE-selectin levels declined rapidly in the Intervention Group while remaining elevated in the Conventional Group suggests that plasmapheresis may modulate endothelial activation. However, as the primary aim of this study was

prognostic rather than interventional, we cannot draw causal conclusions about plasmapheresis efficacy. The Intervention Group data served primarily to highlight the natural trajectory of biomarkers in untreated patients by contrast.

Finally, the integration of biomarker trajectories with clinical scoring systems (e.g., BISAP, APACHE II) [5] and imaging findings [8] may enable development of comprehensive dynamic risk models. Machine learning approaches that incorporate serial biomarker data could potentially outperform static models based on single time points [14].

Limitations. Several limitations must be acknowledged when interpreting these findings. First, the sample size of the Conventional Group (n=32) was modest, and the number of outcome events was small (10 death). This resulted in wide confidence intervals for some estimates, particularly for vWF reflecting statistical uncertainty. The analysis of MOD was especially limited by the small number of events, and these findings should be considered exploratory and hypothesis-generating rather than definitive.

Conclusion

This prospective cohort study demonstrates that endothelial biomarkers sE-selectin and von Willebrand factor provide time-dependent prognostic information in acute pancreatitis. Day 3 sE-selectin ≥56.9 ng/mL emerged as a strong early predictor of in-hospital mortality (AUC 0.905), reflecting acute leukocyte-endothelial interaction during the hyperinflammatory phase. In contrast, Day 7 von Willebrand factor ≥105 U/dL was associated with multiple organ dysfunction (AUC 0.746), indicating persistent endothelial injury and pro-thrombotic alterations. Serial measurements revealed that survivors exhibit declining biomarker trajectories, while non-survivors and patients with organ failure show sustained or rising levels. These findings underscore the importance of time-stratified biomarker assessment rather than single-point measurements for risk stratification in acute pancreatitis.

Prospects for further research. Prospective validation of the proposed cut-off values in larger, multicenter cohorts is warranted, along with investigation of whether biomarker-directed therapeutic interventions, such as targeted endothelial stabilization strategies, can improve clinical outcomes in high-risk patients.

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Conflict of interest. The authors have no conflicts of interest to declare.

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