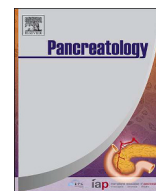




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Systemic inflammation response index (SIRI) predicts outcomes and chemotherapy benefit in metastatic pancreatic cancer: A study by the PANTHEIA- SEOM group

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ABSTRACT

Background: Systemic inflammation is a key driver of progression in pancreatic ductal adenocarcinoma (PDAC). We aimed to externally validate the Systemic Inflammation Response Index (SIRI) and define its non-linear prognostic value in a large multicenter cohort.

Methods: We analyzed 672 patients with metastatic PDAC receiving first-line chemotherapy across 30 centers. SIRI was assessed using a validated cut-off (>2.3) and as a log-transformed continuous variable in multivariable Weibull accelerated failure-time models with restricted cubic splines.

Results: Patients with low SIRI (≤ 2.3) had longer median OS (14.0 vs 9.2 months; $p < 0.001$) and PFS (5.9 vs 3.9 months; $p < 0.001$) than those with high SIRI. High SIRI was associated with a lower objective response rate (25% vs 37%; $p < 0.001$). In multivariable analyses, higher SIRI independently predicted inferior OS and PFS (75th vs 25th percentile: HR 1.14 [95% CI 1.05–1.25], HR 1.11 [95% CI 1.03–1.21]) and

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poorer tumor response (OR 0.78; 95% CI 0.62–1.00). Higher SIRI correlated with greater hepatic tumor burden and cachexia.

Conclusions: SIRI is a robust, independent prognostic marker in metastatic PDAC. Higher values identify a phenotype with inferior survival and poorer tumor response. An open-access web calculator is provided to illustrate and explore the nonlinear, continuous prognostic gradient of SIRI and its impact on outcome.

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1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) remains one of the most lethal malignancies, particularly in the metastatic setting, where five-year overall survival (OS) rates remain below 5% [1]. Despite combination chemotherapy regimens such as gemcitabine plus nab-paclitaxel [2] and FOLFIRINOX [3], clinical outcomes remain suboptimal and treatment-related toxicity is substantial.

A defining hallmark of PDAC is the presence of a pronounced pro-inflammatory state, locally within the tumor microenvironment and systemically [4–6]. Locally, inflammatory cytokines and chemokines secreted by tumor cells and stromal components promote immune evasion, angiogenesis, and epithelial-to-mesenchymal transition [7]. Systemically, this inflammatory response is intertwined with cancer cachexia, a highly prevalent syndrome characterized by involuntary weight loss and skeletal muscle depletion [8]. Cachexia represents a state of chronic systemic inflammation driven by tumor-derived factors that activate NF- κ B and STAT3 signaling pathways [9], leading to sustained production of pro-inflammatory cytokines, including IL-6, TNF- α , and IFN- γ [10]. IL-6 plays a pivotal pleiotropic role, exerting both anabolic and catabolic effects depending on its concentration [10].

This inflammatory milieu reflects a broader immune activation state with a dual and seemingly paradoxical role. On one hand, a certain degree of immune activation appears necessary for chemotherapy-induced tumor cell death and the generation of immunogenic signals [11]. In PDAC, regimens such as FOLFIRINOX have been associated with increased infiltration of CD8⁺ T cells, supporting a role for therapy-induced immune activation [12]. On the other hand, excessive or dysregulated systemic inflammation reflects a state of host exhaustion, associated with functional decline, poor tolerance to treatment, and inferior survival [6].

These limitations and the complexity of the inflammatory landscape highlight the urgent need for biomarkers capable of capturing the underlying biological heterogeneity of the disease to guide therapeutic decision-making. While cytokine profiling offers detailed insight, it is often impractical for routine clinical use. Consequently, inflammation-based biomarkers derived from routine peripheral blood counts have emerged as accessible alternatives. Simple ratios, such as the neutrophil-to-lymphocyte ratio (NLR), have been widely explored; however, more comprehensive indices may better capture the dynamic balance between pro-tumoral inflammation and anti-tumoral immune response.

In this context, the Systemic Inflammation Response Index (SIRI), based on neutrophil, monocyte, and lymphocyte counts, integrates both innate immune activation and adaptive immune suppression [13–16]. Previous work by the PANTHEIA-SEOM research group identified SIRI as an independent prognostic factor in metastatic pancreatic cancer, outperforming traditional parameters such as tumor stage or CA 19-9 [13]. Moreover, elevated SIRI values have been linked to increased levels of cancer-related cytokines, suggesting it acts as a surrogate for the inflammatory cytokine network [16].

Currently, the precise contribution of SIRI relative to other

inflammatory indices and its interaction with chemotherapy efficacy requires further validation. The aim of this study is to validate the prognostic value of SIRI in a metastatic PDAC cohort, determine how it modulates the effect of chemotherapy, compare its performance against other established inflammatory indices, and develop a prognostic calculator to optimize patient stratification.

2. Materials and methods

2.1. Study design, population and data collection

PANTHEIA-SEOM is a multicenter observational cohort study conducted across 30 hospitals in Spain promoted by the outcomes research and clinical practice section of the Spanish Society of Medical Oncology (SEOM). The study utilizes the "Pandora" platform, a SEOM-proprietary web-based electronic case report form (eCRF), for centralized data collection. The present analysis was conducted in an independent, purpose-built multicenter cohort assembled through this registry (30 centers, 2015–2025) and is distinct from, and substantially larger than, the earlier single-center pilot (proof-of-concept) study of 50 patients (2020–2023) from which the SIRI cut-off was originally derived; only the pre-specified cut-off, and not the patients, was carried forward into the present validation.

Clinical, pathological, and laboratory data were retrieved from electronic medical records. The study was conducted in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines. Additionally, the evaluation of prognostic factors and biomarker reporting adhered to the REMARK (Reporting Recommendations for Tumor Marker Prognostic Studies) guidelines [17,18] ([Supplementary Tables 1 and 2](#)).

We included consecutive patients aged ≥ 18 years with histologically or cytologically confirmed metastatic PDAC who initiated systemic chemotherapy in routine clinical practice between 2015 and 2025.

Key exclusion criteria were: (I) presence of a synchronous second primary malignancy; (II) absence of baseline clinical or analytical data required for inflammatory index calculation; and (III) inability to undergo follow-up.

The study protocol was approved by the Ethics Committees of all participating centers and adhered to the Declaration of Helsinki and ICH Good Clinical Practice guidelines. Regarding informed consent, written authorization was obtained from patients who were alive at the time of data collection. For patients who were deceased or lost to follow-up, the requirement for informed consent was waived by the Ethics Committees, ensuring strict data pseudonymization in compliance with the General Data Protection Regulation (GDPR) (EU) 2016/679.

2.2. Objectives

The primary objective was to externally validate the prognostic utility of SIRI using a previously established cut-off in a

multicenter cohort of patients with metastatic PDAC receiving first-line chemotherapy.

Secondary objectives aimed to refine the biological and clinical application of SIRI. First, we examined the association between systemic inflammation and key clinicopathological features, including cancer cachexia and tumor burden. Second, we moved beyond binary classification and evaluated SIRI as a continuous variable to capture the full spectrum of inflammatory risk and its independent prognostic value. Third, we explored potential interactions between inflammatory status and first-line chemotherapy regimens and translated these findings into an accessible clinical calculator for individualized risk stratification.

2.3. Variables and endpoints

SIRI was evaluated as the primary biomarker of interest, calculated from absolute neutrophil (N), monocyte (M), and lymphocyte (L) counts obtained from baseline peripheral blood samples collected within 14 days prior to chemotherapy initiation. Adhering to the standard formula $SIRI = (N \times M) / L$, we employed a comprehensive dual evaluation strategy to maximize both clinical applicability and biological insight. First, patients were stratified into low ($SIRI \leq 2.3$) and high ($SIRI > 2.3$) risk groups, strictly adhering to the validated cut-off established in the original derivation study to assess external reproducibility [13]. Second, to refine prognostic precision and capture the full biological spectrum of systemic inflammation beyond a fixed threshold, SIRI was assessed as a continuous variable in the regression models [19].

All biomarkers used to derive SIRI were obtained from routine complete blood counts performed as part of standard clinical care at each participating center. Hemograms were processed in accredited hospital laboratories using automated hematology analyzers under each site's usual operating procedures, including internal daily quality controls and participation in external proficiency testing programs, with results reported as absolute counts ($\times 10^9/L$). No study-specific reagents, kits, or centralized retesting were required. SIRI was calculated centrally from the recorded absolute cell counts using the prespecified formula; it was not a routinely reported clinical variable and was not disclosed to treat clinicians or outcome assessors. Therefore, clinical decisions and endpoint ascertainment were not intended to be influenced by knowledge of SIRI, minimizing the risk of measurement-related bias.

To ensure robust effect estimates, potential confounding variables for multivariable adjustment were selected a priori based on theoretical relevance and established prognostic literature. The final models included Eastern Cooperative Oncology Group Performance Status (ECOG-PS) (dichotomized as 0–1 vs. ≥ 2), tumor burden (quantified as the sum of target lesion diameters and dichotomized at 5 cm), chemotherapy regimen, and the clinical presence of cancer anorexia-cachexia syndrome (cancer cachexia) [20]. Cancer cachexia was defined according to the Fearon criteria, and was considered present at baseline if at least one of the following conditions was met: unintentional weight loss $>5\%$ during the previous 6 months; or weight loss $>2\%$ in patients with a body mass index $<20 \text{ kg/m}^2$; or weight loss $>2\%$ in the presence of sarcopenia documented by validated methods [20].

Study endpoints were defined in adherence to standard oncology guidelines. OS was calculated as the time elapsed from the date of the first chemotherapy administration to the date of death from any cause; patients who remained alive at the time of the final analysis were censored at the date of last contact. Progression-Free Survival (PFS) was defined as the time from treatment initiation to the first documentation of radiological or clinical disease progression or death from any cause, whichever

occurred first, with censoring applied to patients who were alive and progression-free at the last follow-up. Tumor response was assessed radiologically according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [21], with Objective Response Rate (ORR) defined as the proportion of patients achieving a confirmed complete (CR) or partial response (PR) [21].

2.4. Statistical analysis

Categorical variables were summarized as frequencies and percentages, while continuous variables were reported as medians with interquartile ranges (IQR). Baseline characteristics were compared across groups using the Chi-squared test and the Mann-Whitney *U* test, as appropriate. SIRI exhibited a non-normal distribution and was therefore log-transformed prior to analysis. Box-Cox transformation analysis identified the natural logarithm as the optimal transformation for achieving normality and stabilizing variance (Supplementary Fig. S1). Survival curves were estimated using the Kaplan-Meier method. To maximize data efficiency and minimize bias, missing baseline covariates were handled using Multiple Imputation by Chained Equations (MICE) [22].

For multivariable analysis, Weibull Accelerated Failure Time (AFT) models were fitted for PFS and OS. The AFT parameterization directly models covariate effects on survival time, yielding Time Ratios (TR) that represent the multiplicative change in expected survival time (e.g., $TR = 0.80$ indicates 20% shorter survival). Hazard Ratios (HR) were derived using $HR = TR^{(-1/\sigma)}$, where σ is the Weibull scale parameter. Both metrics are reported; $TR < 1$ and $HR > 1$ indicate worse prognosis [23]. The main effect of $\log(SIRI)$ was modeled flexibly using a restricted (natural) cubic spline with one internal knot and boundary knots, whereas treatment-effect heterogeneity was assessed by including linear chemotherapy regimen-by- $\log(SIRI)$ interaction terms; models were adjusted for prespecified baseline prognostic covariates. Binary outcomes (tumor response) were analyzed using multivariable logistic regression with the same covariate structure, and interaction terms were used to formally test for differential associations across regimens. Biomarker performance was evaluated using the Akaike Information Criterion (AIC) and Harrell's C-index. Model selection followed the Burnham & Anderson criteria, where a $\Delta AIC < 2$ was considered a statistical tie [24].

The study was planned to ensure an adequate number of OS events. Using the Schoenfeld method (two-sided $\alpha = 0.05$, 80% power, approximately balanced groups), ~450 deaths were required to detect a clinically relevant hazard ratio of about 1.30; the available cohort provided a similar number of death events.

All statistical tests were two-sided, with $P < 0.05$ indicating statistical significance. Analyses were performed using R statistical software (v4.3), leveraging the rms and Hmisc packages [25,26] to ensure adherence to robust modeling strategies established in the statistical literature [27]. Prespecified sensitivity analyses assessed the robustness of the $\log(SIRI)$ association with survival to enrolment period (adding the calendar year of first-line initiation and a $\log(SIRI)$ -by-period interaction, 2015–2022 vs 2023–2025), to the receipt of second-line systemic therapy, and to the presence of liver metastases; the fraction of the SIRI effect mediated by cancer cachexia was estimated by comparing SIRI coefficients in models fitted with and without cachexia.

To promote transparency and ensure seamless reproducibility, the complete statistical source code and datasets are openly available in a public GitHub repository archived via Zenodo (<https://github.com/albertocarm/pantheia>; <https://doi.org/10.5281/zenodo.18444522>) [28], allowing full reproduction of all figures and tables presented in this manuscript. Furthermore, an interactive web-based calculator was developed to enable

dynamic exploration of the model predictions (<https://pantheia-siri.shinyapps.io/calculator/>).

3. Results

3.1. Patients & outcomes

Among the 728 patients identified in the PANTHEIA-SEOM registry, 672 had sufficient data for SIRI calculation and constituted the evaluable population (Supplementary Fig. S2 and Table 1). The median age was 65.8 years, and 84.1% of patients had an ECOG-PS of 0 or 1. Despite this preserved functional status, the cohort exhibited a substantial disease burden: 66.2% presented hepatic metastases, and 68.5% reported weight loss greater than 5% at diagnosis. First-line therapy consisted of gemcitabine plus nab-paclitaxel (58.3%), whereas FOLFIRINOX was administered to 23.8% of the study population.

At the time of data cutoff, the median follow-up was 42.9 months (95% CI: 32.8–NR). Among the 593 patients analyzed, 475 deaths (80.1%) had occurred. The median OS was 9.92 months (95% CI: 9.10–10.70). A total of 529 progression or death events were recorded, yielding a median PFS of 5.55 months (95% CI:

4.99–5.98). Tumor response was evaluable in 553 patients. The ORR was 34.7% (n = 192), comprising 12 (2.2%) CR and 180 (32.6%) PR. The Disease Control Rate (DCR) was 61.1% (n = 338), with 146 (26.4%) patients achieving stable disease (SD) as their best response. Progressive disease (PD) was observed in 213 (38.5%) cases. The stepwise reduction from the 672 patients with a computable SIRI to the 593 included in the time-to-event analyses and the 553 evaluable for radiological response reflected the data-availability requirements of each endpoint rather than selective attrition; the 79 patients not analyzed for survival were those whose outcome data were not yet available at the data cut-off, rather than survivors excluded for short follow-up, and the reasons for exclusion at each step are detailed in Supplementary Fig. S2.

3.2. Characterization of patients by SIRI levels

Associations between SIRI levels and clinical characteristics are shown in Supplementary Fig. S3–S5. Patients with asthenia had higher SIRI values than those without (median, 2.34 vs. 1.92; p = 0.009), and a similar association was observed in patients with cancer cachexia (median, 0.77 vs. 0.60; p = 0.043) (Supplementary Fig. S3).

SIRI levels were strongly associated with hepatic involvement. Patients with liver metastases presented significantly higher SIRI values compared with those without liver disease (median, 2.27 vs. 1.77; p < 0.001), with a graded increase according to liver tumor burden, from a median SIRI of 1.99 in patients with <25% liver involvement to 6.17 in those with >75% involvement (p < 0.001) (Supplementary Fig. S4). Obstructive jaundice was also associated with differences in SIRI levels (p = 0.026).

Baseline demographic and lifestyle factors were additionally associated with SIRI. Higher values were observed in male patients, in those with worse performance status (ECOG-PS ≥ 2 vs. 0: median, 2.92 vs. 1.82; p < 0.001), in physically inactive patients (median, 2.41 vs. 1.72; p = 0.002), and across smoking categories, with increasing SIRI values among current smokers (p = 0.025 for trend) (Supplementary Fig. S5).

3.3. Prognostic validation of discretized SIRI

In validation analysis, a SIRI cutoff of >2.3 successfully discriminated prognosis in terms of both OS and PFS (Fig. 1A and B), as well as tumor response (Fig. 1C). Patients with low SIRI (≤2.3) exhibited a significantly prolonged median OS of 14.0 months (95% CI: 12.6–16.5) compared to 9.2 months (95% CI: 7.7–10.2) in the high SIRI group (p < 0.001), a survival benefit that appeared consistent across all treatment regimens analyzed (Table 2). Similarly, median PFS was significantly superior in the low SIRI cohort (5.9 months [95% CI: 5.3–6.8] vs. 3.9 months [95% CI: 2.9–4.8]; p < 0.001).

Regarding treatment response, ORR was higher in the low SIRI group (37% vs 25%; p < 0.001). The impact of systemic inflammation appeared particularly pronounced in the gemcitabine plus nab-paclitaxel subgroup, where ORR decreased from 45.6% in patients with low SIRI to 27.2% in those with high SIRI (p < 0.001). In the FOLFIRINOX cohort, patients with low SIRI also showed a trend toward lower rates of progressive disease (22.7%) than those with high SIRI (37.5%) (p = 0.130) (Table 2).

3.4. Multivariable nonlinear modeling using SIRI

Multivariable AFT models for PFS and OS and logistic regression for tumor response (RECIST) were fitted using pooled estimates from multiple imputation. After adjustment for tumor diameter,

Table 1
Baseline characteristics of the study population.

Characteristic	N = 672
Age, years, median (range)	65.8 (25.8–90.1)
Sex, n (%)	
Male	349 (53.2%)
Female	307 (46.8%)
Unknown/missing	16 (2.4%)
ECOG-PS, n (%)	
0	159 (23.9%)
1	400 (60.2%)
2	96 (14.4%)
≥3	10 (1.5%)
Unknown/missing	7 (1.0%)
Smoking status, n (%)	
Never smoker	285 (42.8%)
Former smoker	187 (28.1%)
Current smoker	194 (29.1%)
Alcohol consumption, n (%)	317 (49.5%)
Prolonged steroid use, n (%)	13 (1.9%)
Familial cancer syndrome, n (%)	38 (6.1%)
Symptoms and syndromes, n (%)	
Asthenia	330 (49.3%)
Anorexia	297 (44.4%)
Weight loss >5%	458 (68.5%)
Cachexia	78 (11.7%)
Tumor location, n (%)	
Head of the pancreas	328 (48.8%)
Body/Tail of the pancreas	344 (51.2%)
Disease status, n (%)	
Liver metastasis	445 (66.2%)
Peritoneum metastasis	204 (30.4%)
Locoregional LN metastasis	163 (24.3%)
Lung metastasis	158 (23.5%)
Inflammation marker, n (%)	
Elevated SIRI (>2.3)	307 (45.7%)
First-line regimen, n (%)	
FOLFIRINOX	160 (23.8%)
Gem-NabP	392 (58.3%)
Gemcitabine mono	75 (11.2%)
Other	45 (6.7%)

Abbreviations: ECOG-PS, Eastern Cooperative Oncology Group Performance Status; CACS, cancer anorexia cachexia syndrome; LN, Lymph Node; SIRI, Systemic Inflammation Response Index; Gem-NabP, Gemcitabine plus Nab-Paclitaxel; FOLFIRINOX, 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin.

Footnotes: Data are presented as n (%) unless otherwise specified as median (range). Percentages may not total 100% due to rounding or missing data in specific categories.

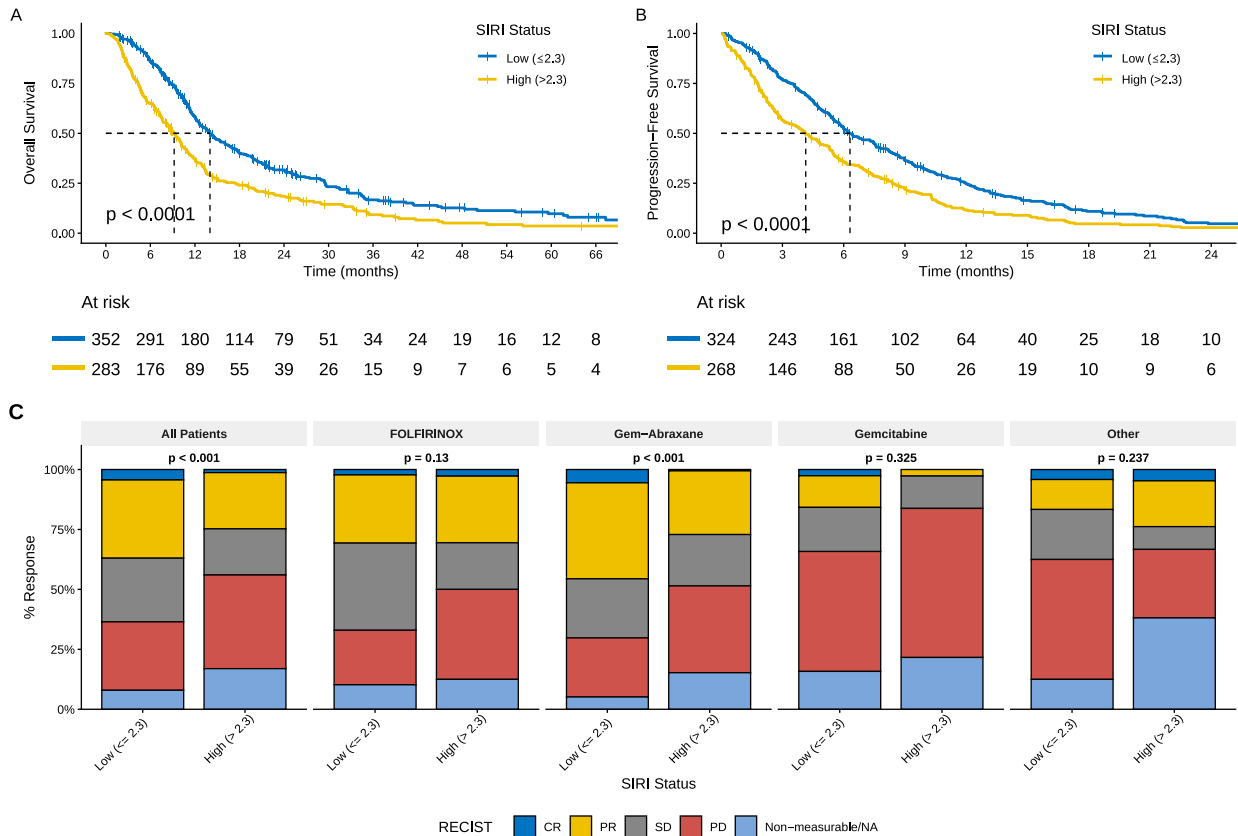


Fig. 1. Prognostic value of baseline SIRI in patients with metastatic pancreatic adenocarcinoma. Abbreviations: CR, complete response; Gem-NabP, Gemcitabine plus Nab-Paclitaxel; NA, not available; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; SIRI, systemic inflammation response index. Footnotes: Kaplan-Meier curves for OS (A) and PFS (B) stratified by baseline SIRI status using a cutoff of 2.3. Panel C shows the distribution of best ORR according to RECIST 1.1 criteria by SIRI status and chemotherapy regimen. P-values were calculated using the log-rank test for survival endpoints and chi-square test for response comparisons.

Table 2

Treatment response and survival outcomes according to SIRI status across different chemotherapy regimens.

Subgroup	SIRI Status	N	CR n (%)	PR n (%)	SD n (%)	PD n (%)	ORR (CR + PR)	DCR (CR + PR + SD)	P (Chi ²)	mOS (months) [95% CI]	P (Log-Rank)	mPFS (months) [95% CI]	P (Log-Rank)
Global Cohort	Low (≤ 2.3)	365	16 (4.4%)	119 (32.6%)	97 (26.6%)	104 (28.5%)	37.0%	63.6%	< 0.001	14.0 [12.6–16.5]	< 0.001	5.9 [5.3–6.8]	< 0.001
	High (> 2.3)	307	4 (1.3%)	72 (23.5%)	59 (19.2%)	120 (39.1%)	24.8%	44.0%		9.2 [7.7–10.2]		3.9 [2.9–4.8]	
FOLFIRINOX	Low (≤ 2.3)	88	2 (2.3%)	25 (28.4%)	32 (36.4%)	20 (22.7%)	30.7%	67.0%	0.130	17.0 [11.4–25.1]	0.144	8.1 [5.4–10.2]	0.097
	High (> 2.3)	72	2 (2.8%)	20 (27.8%)	14 (19.4%)	27 (37.5%)	30.6%	50.0%		10.2 [9.5–13.3]		5.0 [4.0–7.8]	
Gem-Abraxane	Low (≤ 2.3)	215	12 (5.6%)	86 (40.0%)	53 (24.7%)	53 (24.7%)	45.6%	70.2%	< 0.001	13.8 [12.2–16.1]	< 0.001	6.2 [5.5–7.5]	< 0.001
	High (> 2.3)	177	1 (0.6%)	47 (26.6%)	38 (21.5%)	64 (36.2%)	27.2%	48.6%		9.3 [7.6–11.4]		4.0 [2.8–5.3]	
Gemcitabine	Low (≤ 2.3)	38	1 (2.6%)	5 (13.2%)	7 (18.4%)	19 (50.0%)	15.8%	34.2%	0.325	10.8 [8.4–14.3]	0.039	4.1 [2.8–5.7]	0.481
	High (> 2.3)	37	0 (0.0%)	1 (2.7%)	5 (13.5%)	23 (62.2%)	2.7%	16.2%		5.4 [4.1–9.8]		2.5 [1.5–4.0]	
Others	Low (≤ 2.3)	24	1 (4.2%)	3 (12.5%)	5 (20.8%)	12 (50.0%)	16.7%	37.5%	0.237	23.9 [19.8–50.0]	0.012	2.0 [0.2–17.1]	0.156
	High (> 2.3)	21	1 (4.8%)	4 (19.0%)	2 (9.5%)	6 (28.6%)	23.8%	33.3%		7.7 [3.2–NR]		1.8 [1.3–9.1]	

Abbreviations: SIRI, Systemic Inflammation Response Index; CR, Complete Response; PR, Partial Response; SD, Stable Disease; PD, Progressive Disease; ORR, Objective Response Rate (CR + PR); DCR, Disease Control Rate (CR + PR + SD); mOS, median Overall Survival; mPFS, median Progression-Free Survival; 95% CI, 95% Confidence Interval; NR, Not Reached. P (Chi²) values were calculated using the Chi-square test (or Fisher's exact test where appropriate) to compare response rates between SIRI groups. P (Log-Rank) values represent the significance of differences in survival curves between low and high SIRI status using the Kaplan-Meier method. Statistically significant differences are defined as $P < 0.05$.

ECOG-PS, cancer cachexia, and chemotherapy regimen, log (SIRI) remained independently associated with both PFS, OS, and ORR. The estimates for the main effects across the three study endpoints are summarized in Fig. 2. Comparing the 75th to the 25th percentile of log (SIRI) (corresponding to SIRI values of 4.0 vs 1.15), the adjusted HR was 1.11 (95% CI: 1.03–1.21; $p = 0.01$) for PFS and 1.14 (95% CI: 1.05–1.25; $p = 0.003$) for OS. Furthermore, higher log (SIRI) levels were associated with a lower likelihood of ORR (OR 0.78; 95% CI: 0.62–1.00; $p = 0.05$). ECOG-PS was a significant independent predictor of both PFS and OS. Compared with ECOG-PS 0, patients with ECOG-PS 1 had significantly worse OS (HR 1.51, 95% CI: 1.16–1.97; $p = 0.002$) but not PFS (HR 1.15, 95% CI: 0.90–1.46; $p = 0.254$). Patients with ECOG-PS ≥ 2 had markedly worse outcomes for both PFS (HR 2.02, 95% CI: 1.48–2.75; $p < 0.001$) and OS (HR 2.45, 95% CI: 1.74–3.45; $p < 0.001$). Cancer cachexia was also independently associated with shorter PFS (HR 1.35, 95% CI: 1.09–1.68; $p = 0.006$) and OS (HR 1.60, 95% CI: 1.27–2.01; $p < 0.001$). Tumor diameter >5 cm showed a borderline association with PFS (HR 0.81, 95% CI: 0.66–1.00; $p = 0.055$) but not with OS (HR 0.91, 95% CI: 0.72–1.15; $p = 0.421$). Exploratory analyses including regimen-specific slopes (log (SIRI)-by-regimen interaction) showed broadly comparable effect estimates across treatment groups (Supplementary Material S1: Multivariable Prognostic Models), although the study was not powered to detect differential effects. The association between log (SIRI) and survival outcomes was nonlinear (nonlinearity test $p = 0.004$ for PFS, $p < 0.001$ for OS), with hazard ratios increasing more steeply at higher SIRI values, suggesting a threshold effect where elevated systemic inflammation confers progressively greater risk. Fig. 3 illustrates the non-linear association between log (SIRI) and survival outcomes, with a steeper risk gradient at higher SIRI values. The direction and shape of this association were consistent in the overall cohort and across first-line chemotherapy regimens. To facilitate clinical application, including potential subgroup effects, an interactive web calculator providing patient-specific predictions for PFS, OS, and ORR probability based on these models is available at <https://pantheia-siri.shinyapps.io/calc/>.

In prespecified sensitivity analyses, the prognostic association of SIRI with outcome was robust. It was consistent across enrolment periods, with no significant interaction between log (SIRI) and calendar period (2015–2022 vs 2023–2025; interaction $p = 0.45$ for OS and $p = 0.95$ for PFS), and it was essentially unchanged after additional adjustment for the calendar year of

treatment initiation or for the receipt of second-line therapy. Adjustment for cancer cachexia altered the log (SIRI) coefficient by less than 5%, indicating that cachexia mediated only a negligible fraction of its prognostic effect. The effect of SIRI was directionally consistent in patients with and without liver metastases (interaction $p = 0.44$ for OS and $p = 0.42$ for PFS); within the subgroup with liver metastases, higher SIRI further identified patients less likely to respond to chemotherapy (objective response 30.4% vs 43.6% for high vs low SIRI; $p = 0.013$).

3.5. Identification of SIRI as the most robust prognostic indicator

Finally, the comparative analysis of log-transformed indices identified SIRI as the optimal global predictor among several inflammation-based indices, including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), and derived equivalents (Supplementary Material S2: Comparative Analysis and Selection of Inflammatory Biomarkers). SIRI demonstrated significantly superior model fit for OS compared to the runner-up and statistical equivalence to the top-ranked indices in PFS and ORR.

4. Discussion

In this multicenter real-world cohort of metastatic PDAC, we evaluated SIRI as a prognostic biomarker and refined its clinical applicability using nonlinear modeling as a continuous variable. Higher SIRI was consistently associated with shorter OS and PFS and with lower treatment response across contemporary chemotherapy regimens, supporting its prognostic relevance beyond treatment backbone. The median OS was 14.0 months (95% CI 12.6–16.5) in the low-risk group, consistent with independent datasets, including the 13.4 months reported by Kamposioras et al. [29] and the ~16 months observed in our preliminary derivation cohort. In contrast, high SIRI (>2.3) was associated with poor outcomes (OS 9.2 months [95% CI: 7.7–10.2]; PFS 3.9 months [95% CI: 2.9–4.8]).

We further characterized the clinical implications of high versus low inflammatory states. First, we previously hypothesized that marked systemic inflammation might identify a subgroup more likely to benefit from treatment intensification [14,15]. However, our multicenter analysis suggests that elevated SIRI primarily captures a poor-prognosis phenotype with unfavorable

Multivariable Analysis of Outcomes

Forest plot showing Hazard Ratios (HR) and Odds Ratios (OR)

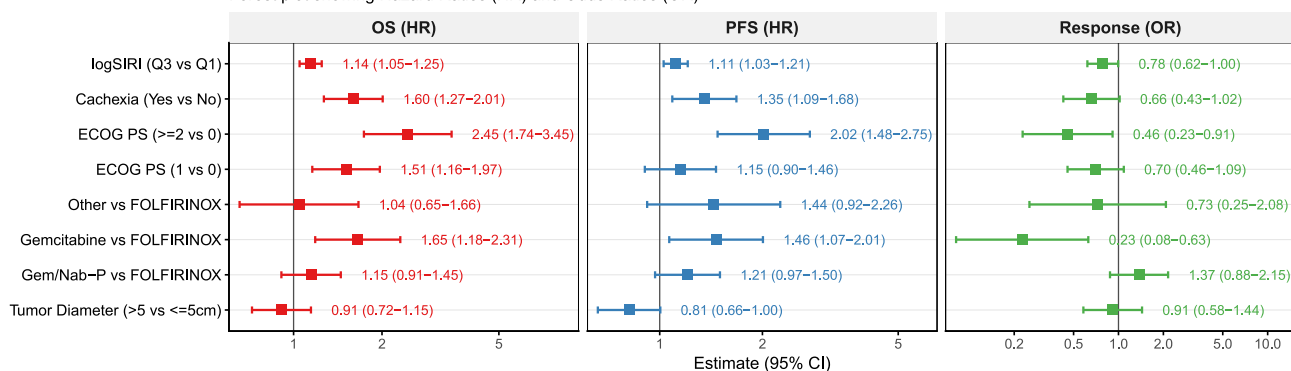


Fig. 2. Forest plot of multivariable analysis for survival and response outcomes. Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; Gem/Nab-P, Gemcitabine plus Nab-Paclitaxel; FOLFIRINOX, Leucovorin, Fluorouracil, Irinotecan, and Oxaliplatin; OS, Overall Survival; PFS, Progression-Free Survival. Footnotes: The figure displays the independent association of baseline characteristics with PFS, OS, and response. Squares represent point estimates, and horizontal lines indicate 95% confidence intervals (95% CI). For survival outcomes (PFS and OS), estimates are presented as Hazard Ratios (HR); for tumor response, estimates are presented as Odds Ratios (OR). The effect of the Systemic Inflammation Response Index (SIRI) is shown comparing the 75th percentile (Q3) to the 25th percentile (Q1) of the log-transformed distribution.

Effect of logSIRI: Global (Main Effects) vs Regimens

Top Row: Main Effects Models (No interaction). Other Rows: Interaction Models.

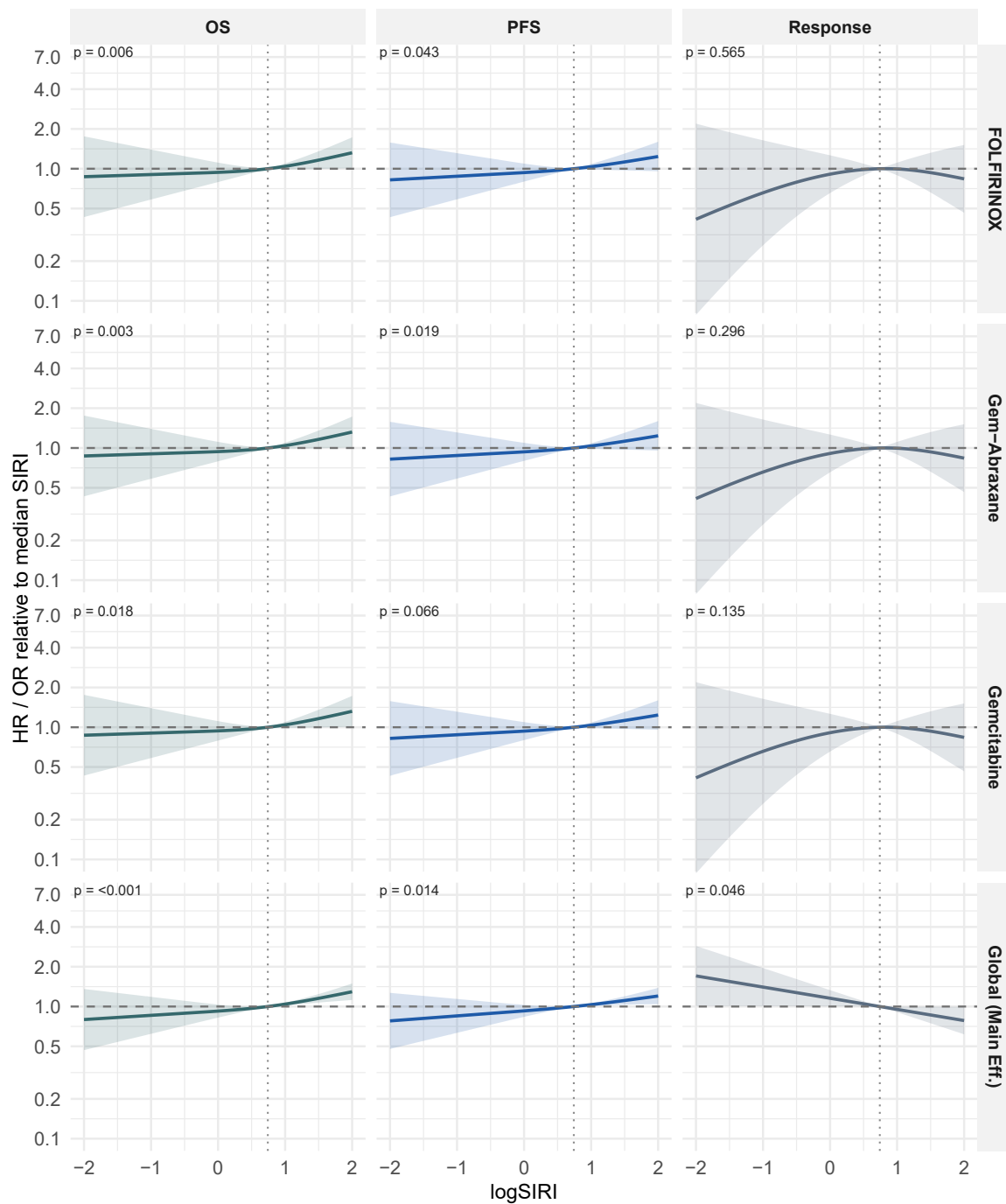


Fig. 3. Global and Regimen-Specific Associations Between logSIRI and Clinical Outcomes. Abbreviations: Gem-Abraxane, gemcitabine plus nab-paclitaxel; HR, hazard ratio; logSIRI, log-transformed systemic inflammation response index; OR, odds ratio; OS, overall survival; PFS, progression-free survival. Footnotes: Restricted cubic spline analysis showing the relationship between logSIRI (log-transformed SIRI) and hazard ratios for progression-free survival and overall survival, and odds ratios for objective response. The bottom row ("Global (Main Eff.)") displays estimates from multivariable main-effects models (without interaction terms). The upper rows display regimen-specific estimates derived from models including a logSIRI-by-regimen interaction term. Hazard ratios and odds ratios are expressed relative to the median logSIRI value within each panel. Shaded areas represent 95% confidence intervals. P-values indicate the statistical significance of the association (linear or non-linear) for the global population or within each regimen subgroup.

outcomes across chemotherapy backbones. Although FOLFIRINOX yielded a numerically higher median OS (10.2 months) than gemcitabine plus nab-paclitaxel (9.3 months) in the high-risk group, the overlap in confidence intervals supports the

interpretation that severe systemic inflammation may limit the incremental benefit of cytotoxic intensification in this setting.

Second, while dichotomizing patients into "high" versus "low" risk is clinically convenient, it may obscure the more granular

relationship between inflammation and survival. Prior reports have proposed different SIRI cut-offs (e.g., 1.8 or 2.3) [16,30], complicating comparability across series. Our analysis addresses this issue by showing that SIRI behaves as a continuous risk metric without an apparent “safe” plateau, with progressively worse outcomes as inflammatory burden increases [19]. Clinically, this implies that a patient with SIRI 4.0 is meaningfully distinct from one with SIRI 2.5, a nuance not captured by binary thresholds. To facilitate translation into practice, we implemented an open-access web calculator (Shiny [app](#)) that integrates the nonlinear estimates to provide estimated survival probabilities across the SIRI continuum.

Third, the strong association between elevated SIRI and cancer cachexia provides a biologically plausible framework for its prognostic performance. Cachexia is common in PDAC and contributes to poor outcomes, treatment intolerance, and early mortality [8,10]. Inflammatory biomarkers, including C-reactive protein and neutrophil-based indices, have been consistently linked to cachexia severity and survival in PDAC [31–33]. In this context, our findings support the concept that systemic inflammation parallels metabolic decline, as cachexia itself represents a complex inflammatory syndrome extending beyond nutritional impairment alone. Importantly, SIRI retained prognostic value independent of cachexia status, suggesting that it captures aspects of systemic inflammatory burden not fully encompassed by clinical cachexia definitions. This may reflect either greater biological heterogeneity within cachectic states or the ability of SIRI to identify earlier or subclinical inflammatory phases, such as pre-cachexia. Consequently, SIRI appears to provide incremental prognostic information across baseline nutritional and metabolic profiles by quantifying systemic inflammation along a broader disease continuum. Because SIRI and cancer cachexia are biologically intertwined and may share a common causal pathway, we examined whether cachexia acted as a mediator rather than a confounder of the SIRI–survival association; adjustment for cachexia changed the SIRI estimate by less than 5%, indicating that only a negligible fraction of its prognostic effect is mediated by clinically defined cachexia and that the two variables capture partly distinct dimensions of systemic inflammation.

Fourth, elevated SIRI was also associated with a higher aggregate burden of disease and functional impairment, including extensive liver metastases, obstructive jaundice, and poor ECOG-PS. This pattern supports SIRI as an integrative marker of the disease–host interaction, linking anatomical tumor burden with systemic host response. Hepatic involvement may be a relevant amplifier of systemic inflammation. Liver metastases can remodel the hepatic microenvironment through macrophage polarization and cytokine release that extends into the systemic circulation [34], contributing to increased neutrophil and monocyte counts. Consistent with broader evidence connecting inflammation with aggressive tumor biology [35], our results align with the concept that SIRI reflects both tumor burden and host physiological reserve.

Fifth, our continuous modeling is compatible with the view that excessive inflammation may reflect a state of host exhaustion that compromises the effectiveness of systemic therapy. While some degree of immune priming may contribute to chemotherapy response [36,37], the present data suggest that any such benefit is attenuated as inflammatory burden rises, consistent with a clinical phenotype characterized by metabolic and immune dysregulation.

Beyond PDAC, SIRI has been associated with tumor aggressiveness and clinical outcomes across several malignancies, including ovarian [38], cervical [39], head and neck [40], and colorectal cancers [41]. Across these settings, higher SIRI has generally correlated with more advanced disease and worse

survival, and in some reports its integration into prognostic models has improved risk stratification beyond conventional clinicopathological variables [41], supporting the broader relevance of systemic inflammation-based biomarkers.

This study has limitations. Its observational design and the heterogeneity of real-world treatment patterns introduce the possibility of residual confounding despite multiple imputation and multivariable adjustment. In addition, independent external validation in separate cohorts remains needed. Finally, integration of ongoing PANTHEIA translational research with molecular and nutritional biomarkers may help further define the role of SIRI within a more comprehensive precision-oncology framework. Although enrolment spanned a decade, the first-line treatment options in metastatic PDAC (FOLFIRINOX and gemcitabine plus nab-paclitaxel) were already established at the start of the study period, and the prognostic effect of SIRI was consistent across enrolment periods with no significant interaction with calendar time; nonetheless, gradual changes in supportive care and disease trajectory over time cannot be entirely excluded.

From a clinical perspective, SIRI has practical appeal because it is routinely available and low cost. The web-based calculator operationalizes the nonlinear, continuous associations observed here and may support individualized prognostic discussions beyond static risk groups. Importantly, we propose using SIRI not to deny standard-of-care treatment, but to identify a phenotype of “biological frailty” that may warrant earlier, prioritized supportive interventions (particularly nutritional assessment and optimization) and consideration for clinical trials targeting host inflammation. This approach is conceptually aligned with work in resected NSCLC, where SIRI has been incorporated into prognostic nomograms combining clinical and laboratory variables with favorable discriminatory performance [42]. In terms of practical application, SIRI is best regarded as a complementary, continuous prognostic layer rather than a substitute for established factors such as the presence of liver metastases. In our cohort, higher SIRI retained prognostic value for both OS and PFS in patients with and without liver metastases and, among those with liver metastases, further distinguished patients less likely to respond to chemotherapy. These data do not support using SIRI to withhold standard chemotherapy or as a stand-alone stratification factor in randomized trials; rather, they suggest it could serve as a stratification or enrichment variable in trials of host-directed or supportive interventions and could help flag patients for earlier nutritional and supportive care.

Future translational analyses integrating SIRI with molecular profiling, immune and cytokine signatures, and nutritional and metabolic biomarkers will aim to clarify the biological mechanisms underlying its prognostic and predictive relevance. This approach may determine whether elevated SIRI reflects distinct molecular subtypes, inflammatory signaling pathways, or early stages of cachexia-related metabolic dysregulation. Longitudinal assessment of SIRI in prospective cohorts will further evaluate its dynamic association with treatment response, disease progression, and the transition from pre-cachexia to overt cachexia, ultimately supporting more refined risk stratification and biologically informed therapeutic strategies.

In conclusion, SIRI is an accessible, low-cost prognostic biomarker that integrates systemic inflammation and disease burden and is consistently associated with outcomes in metastatic PDAC. The relationship between SIRI and prognosis appears cumulative and nonlinear, indicating that single cut-offs may not fully capture the underlying biological gradient. The accompanying web-based calculator translates these nonlinear estimates into clinically interpretable survival predictions to support research and individualized prognostic discussions. Although

independent external validation is still required, our findings support incorporating SIRI as a continuous measure to refine risk stratification, align therapeutic expectations with patient biology, and prioritize nutritional assessment in metastatic pancreatic cancer.

Author contributions

Conceptualization: ACB, AMM, PJF, VPB, AMM Data curation: AMM, VPB, VPB Formal analysis: ACB, VPB Investigation: AMM, PJF, VPB, AMM, MAVC, MTC, CGP, AL, MB, JG, PCS, RHS, JH, ALo, MLST, IP, JA, IG, EBV, LCG Methodology: ACB, PJF, VPB, AMM Project administration: PJF, VPB, AMM Software: ACB Supervision: PJF, VPB, AMM Validation: ACB, VPB, AMM, PJF Visualization: ACB Writing – original draft: ACB, AMM, PJF, VPB Writing – review & editing: All authors.

All authors have read and approved the final version of the manuscript.

*ACB and AMM contributed equally to this work and share first authorship.

Data availability statement

The datasets analyzed during the current study are not publicly available due to patient privacy considerations but are available from the corresponding author upon reasonable request. The analytical code used in this study is publicly available at GitHub (<https://github.com/albertocarm/pantheia>) and archived in Zenodo (<https://doi.org/10.5281/zenodo.18444522>).

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Conflict of interest statement

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.pan.2026.08.008>.

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