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*Original Article*

# Exploratory evaluation of the systemic inflammatory response index and internally evaluated machine learning models for prognosis in acute pesticide poisoning

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**Abstract:** Purpose: Acute pesticide poisoning (APP) is a life-threatening emergency with substantial mortality. This study aimed to evaluate whether the systemic inflammatory response index (SIRI) is associated with short-term prognosis in APP and to explore whether SIRI-containing machine learning models can support preliminary risk stratification. Because only 17 deaths occurred in this small single-center retrospective cohort and no external validation cohort was available, the analysis was designed and interpreted as exploratory rather than as development of a clinically deployable prediction model. Methods: A total of 127 patients with APP admitted to our hospital between October 2018 and December 2024 were retrospectively enrolled, including 110 survivors and 17 non-survivors. SIRI was calculated as absolute neutrophil count × absolute monocyte count/absolute lymphocyte count. All hypothesis tests were two-sided. Missing laboratory data were handled by complete-case screening for key variables and median imputation for variables with less than 10% missingness in model development. Logistic regression, random forest (RF), and support vector machine (SVM) analyses were performed only as exploratory internal modelling analyses using a predefined 70:30 training-internal hold-out split and repeated 10-fold cross-validation within the training set. Because the hold-out set was small and contained only a few deaths, ROC-derived cut-offs, threshold-dependent sensitivity/specificity, calibration metrics, and decision-curve results were not used as clinical validation evidence. Results: SIRI was lower in the non-survival group than in the survival group (2.4 ± 3.1 vs. 6.1 ± 5.8; two-sided P = 0.042), consistent with the trend shown in Figure 3A. In multivariable logistic regression adjusted for RBC, D-dimer, APTT, AST, creatinine, glucose, albumin, and pesticide type, lower SIRI remained associated with mortality (adjusted OR = 0.86, 95% CI: 0.74-0.99, P = 0.041). However, given the low number of fatal events, the regression estimates, variable selection results, and machine learning performance metrics should be interpreted as statistically unstable candidate signals rather than externally generalizable evidence. Conclusion: Low SIRI was associated with mortality in this single-center APP cohort after adjustment for selected confounders, and exploratory models incorporating SIRI suggested that routine hematological and inflammatory variables may contain preliminary prognostic information. Nevertheless, because the death group included only 17 patients, mechanistic immune-inflammatory assays were not available, and no independent external validation cohort was included, SIRI should be regarded as a candidate blood-count-derived prognostic signal rather than a mechanistically proven biomarker. The RBC-SIRI pattern should not be used for clinical decision-making before prospective multicenter validation, calibration updating, and mechanistic verification.

**Keywords:** Acute pesticide poisoning, systemic inflammatory response index, machine learning, support vector machine, prognosis, mortality

## Introduction

The global incidence of acute pesticide poisoning (APP) has surpassed three million cases annually, representing a formidable public health challenge due to the high morbidity and mortality rates associated with the condition [1]. Given the clinical urgency of these cases, identifying universally applicable indices to predict patient prognosis is essential for effective risk stratification and the optimization of clinical outcomes [2]. The pathological mechanisms of acute organophosphorus poisoning are complex and primarily involve acetylcholinesterase

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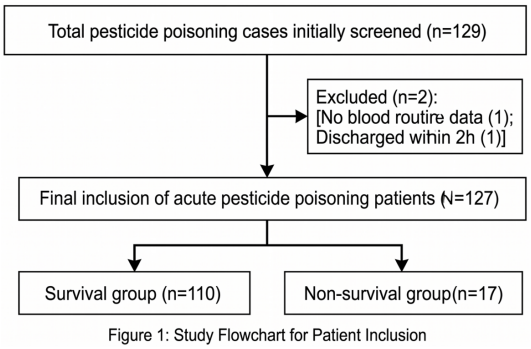


**Figure 1.** Sample screening flowchart.

inhibition alongside profound oxidative stress [3]. These processes have been shown in animal models to trigger significant neurotoxicity and precipitate systemic inflammatory response syndrome (SIRS) [4]. In clinical practice, modulating serum cytokine levels through interventions such as hemoperfusion or continuous renal replacement therapy is considered vital for managing the inflammatory cascade [5]. Furthermore, research indicates that organophosphate toxins can induce specific airway inflammation and mechanical responses that further complicate the clinical picture [6].

Importantly, APP is a heterogeneous toxicological syndrome rather than a single biological entity. Organophosphates, bipyridyl herbicides such as paraquat or diquat, fumigant pesticides such as aluminum phosphide, and rodenticides can differ in primary toxic targets, inflammatory patterns, organ injury profiles, and mortality mechanisms. Therefore, any SIRI-based stratification should be interpreted in relation to pesticide category and should not be generalized across toxicants without adequate stratum-specific clinical data.

Recently, the systemic inflammatory response index (SIRI) has emerged as a clinically useful composite inflammatory marker and has been reported as an independent prognostic factor in several diseases, including post-transplant hepatocellular carcinoma [7]. Updated studies have also demonstrated associations between SIRI and the severity of coronary artery disease and acute coronary syndrome [8]. Within neurological emergencies, SIRI has been used to estimate the severity of secondary complications such as pneumonia [9]. Systematic reviews suggest that inflammatory markers, including SIRI, may have prognostic value in emergency medicine [10]. In APP, however, the observation that non-survivors may have lower rather than higher SIRI is biologically counterintuitive and should be interpreted cautiously. Because SIRI is calculated only from neutrophil, monocyte, and lymphocyte counts, it cannot by itself identify cytokine activation, immune-cell phenotypes, neutrophil function, monocyte polarization, oxidative stress, or toxin-specific inflammatory pathways. Thus, the present study treats low SIRI as a candidate clinical signal rather than direct mechanistic evidence.

With the advancement of computational medicine, machine learning can be used to explore nonlinear interactions among clinical variables in emergency datasets [11-13]. However, prediction-model guidance such as TRIPOD+AI emphasizes transparent reporting, adequate event numbers, evaluation of both discrimination and calibration, and external evaluation before implementation [14]. Because the present cohort contained only 17 deaths and lacked an external validation cohort, the machine learning component was intended to generate preliminary hypotheses and assess internal consistency rather than to establish a ready-to-use clinical prediction tool. Therefore, this study evaluated the association between SIRI and short-term mortality in APP and explored internally evaluated machine learning models as a basis for future prospective multicenter validation.

## Methods

*Retrospective cohort and data collection*

This retrospective cohort included 127 consecutive patients with APP admitted to the First People's Hospital of Wuyi County between October 2018 and December 2024. APP was diagnosed according to a clear history of pesticide exposure, compatible clinical manifestations, and emergency laboratory findings. Patients were excluded if they lacked key routine blood data, were discharged within 2 hours, had malignant hematological disease, active infection before poisoning, or received immunosuppressive therapy before admission. The patient screening process is summarized in **Figure 1**. The primary outcome was in-hospital death. For descriptive analysis, clinical outcomes were initially classified as recovery, sta-

**Table 1.** Baseline clinical data of patients with APP

| Characteristic | Total (N = 127) | Survival Group (n = 110) | Non-Survival Group (n = 17) | *P*-value |
|---|---|---|---|---|
| Pesticide Type [n (%)] | | | | |
| Organophosphates | 111 (87.4) | 99 (90.0) | 12 (70.6) | 0.021 |
| Non-organophosphates | 16 (12.6) | 11 (10.0) | 5 (29.4) | |
| Hematological Indicators | | | | |
| SIRI | 5.6 ± 5.7 | 6.1 ± 5.8 | 2.4 ± 3.1 | 0.042 |
| NLR | 7.0 ± 6.5 | 7.6 ± 6.6 | 2.9 ± 4.5 | 0.013 |
| LMR | 4.0 ± 3.3 | 3.4 ± 2.2 | 8.4 ± 6.5 | 0.04 |
| Neutrophil (%) | 0.7 ± 0.2 | 0.7 ± 0.2 | 0.5 ± 0.2 | 0.011 |
| Lymphocyte (%) | 0.2 ± 0.1 | 0.2 ± 0.1 | 0.4 ± 0.2 | 0.013 |
| Lymphocyte Count ($\times 10^9$/L) | 2.9 ± 2.3 | 2.6 ± 1.9 | 5.7 ± 3.0 | 0.012 |
| RBC ($\times 10^{12}$/L) | 4.7 ± 0.5 | 4.8 ± 0.4 | 3.8 ± 0.4 | < 0.001 |
| HGB (g/L) | 136.9 ± 16.1 | 139.7 ± 13.9 | 118.8 ± 12.3 | < 0.001 |
| Coagulation Markers | | | | |
| D-Dimer (μg/L) | 3583.7 ± 7411.0 | 1534.4 ± 851.5 | 16124.5 ± 19582.6 | 0.007 |
| APTT (s) | 24.8 ± 4.4 | 23.8 ± 3.3 | 31.4 ± 6.2 | 0.002 |
| Biochemical Markers | | | | |
| AST (U/L) | 40.0 ± 81.3 | 26.7 ± 10.5 | 124.9 ± 201.0 | 0.028 |
| Creatinine (μmol/L) | 81.6 ± 28.7 | 79.0 ± 29.8 | 98.1 ± 15.6 | 0.012 |
| Glucose (mmol/L) | 7.1 ± 2.5 | 7.0 ± 2.3 | 8.8 ± 3.0 | 0.038 |
| Albumin (g/L) | 39.7 ± 3.4 | 40.1 ± 3.0 | 36.8 ± 4.1 | 0.008 |
| WBC Count ($\times 10^9$/L) | 10.9 ± 4.6 | 11.0 ± 4.8 | 10.0 ± 2.9 | 0.315 |
| hs-CRP (mg/L) | 2.0 ± 9.3 | 2.0 ± 10.2 | 1.8 ± 1.6 | 0.812 |

Note: The pesticide variable was collapsed as organophosphate versus non-organophosphate for regression because of sparse events; four-category pesticide comparisons were used only for exploratory visualization. Continuous variables are reported using available clinical data and rounded values. These baseline differences should be interpreted as associations rather than causal evidence. Abbreviations: APP, acute pesticide poisoning; SIRI, systemic inflammatory response index; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; RBC, red blood cell count; HGB, hemoglobin; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; WBC, white blood cell count; hs-CRP, high-sensitivity C-reactive protein.

bilization, deterioration, and death; for regression and machine learning analyses, they were converted into survival and non-survival groups because the number of fatal events was limited. Pesticide category was recorded according to the clinical exposure history; sparse non-organophosphate categories were retained only for exploratory visualization and were collapsed into organophosphate versus non-organophosphate exposure for regression analysis.

*Statistical analysis*

APP patients were first divided into four prognostic subgroups (recovery, stabilization, deterioration, and death), and the Kruskal-Wallis test was used for multi-group comparisons. Because the deterioration and death subgroups were small and the clinically most relevant outcome was survival status, the four groups were further combined into survival and non-survival groups for regression analysis and machine learning model construction. Continuous variables were summarized as mean ± standard deviation or median (interquartile range) according to distribution, and categorical variables were summarized as number and percentage. Univariate results were treated as descriptive candidate associations rather than as definitive screening evidence for causal or externally valid predictors.

Candidate variables for exploratory machine learning were restricted to routinely available admission data, including demographic and exposure information, pesticide category, blood routine indices (WBC, NEUT, LYM, MONO, RBC, HGB, RDW, PDW, and MPV), derived inflammatory ratios (SIRI, NLR, and LMR), coagulation markers (APTT, D-dimer, and fibrinogen), and biochemical markers (AST, ALT, creatinine, glucose, albumin, and hs-CRP). Variables not shown in **Table 1** but appearing in the SHAP

**Table 2.** Univariate logistic regression analysis for mortality in APP

| Variable | Odds Ratio (OR) | 95% CI Lower | 95% CI Upper | *P*-value |
|---|---|---|---|---|
| SIRI | 0.82 | 0.68 | 0.99 | 0.042 |
| NLR | 0.78 | 0.65 | 0.94 | 0.011 |
| LMR | 1.35 | 1.02 | 1.78 | 0.035 |
| Neutrophil (%) | 0.61 | 0.42 | 0.89 | 0.013 |
| Lymphocyte (%) | 1.82 | 1.21 | 2.74 | 0.004 |
| Lymphocyte Count ($\times 10^9$/L) | 2.15 | 1.28 | 3.62 | 0.003 |
| RBC ($\times 10^{12}$/L) | 0.12 | 0.05 | 0.29 | < 0.001 |
| HGB (g/L) | 0.85 | 0.79 | 0.92 | < 0.001 |
| D-Dimer (μg/L) | 1.001 | 1.000 | 1.002 | 0.021 |
| APTT (s) | 1.12 | 1.05 | 1.19 | 0.001 |
| AST (U/L) | 1.01 | 1.00 | 1.02 | 0.018 |
| Creatinine (μmol/L) | 1.03 | 1.01 | 1.05 | 0.012 |
| Glucose (mmol/L) | 1.22 | 1.03 | 1.45 | 0.023 |
| Albumin (g/L) | 0.82 | 0.71 | 0.95 | 0.007 |
| WBC Count ($\times 10^9$/L) | 0.96 | 0.82 | 1.12 | 0.612 |
| hs-CRP (mg/L) | 0.98 | 0.89 | 1.08 | 0.715 |

Note: Univariate analyses were descriptive and were used only to identify candidate associations. Because only 17 deaths occurred, variables were not interpreted as stable independent predictors solely on the basis of $P < 0.05$. Abbreviations: APP, acute pesticide poisoning; OR, odds ratio; CI, confidence interval; SIRI, systemic inflammatory response index; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; RBC, red blood cell count; HGB, hemoglobin; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; WBC, white blood cell count; hs-CRP, high-sensitivity C-reactive protein.

plot were therefore part of the prespecified routine laboratory feature set.

Because only 17 fatal events were available, all multivariable regression and machine learning analyses were prespecified as exploratory. The multivariable model was limited to clinically relevant covariates selected from univariate findings and collinearity screening, but the resulting odds ratios were not considered definitive independent effects. The random training-internal hold-out split was used only for apparent internal evaluation and model interpretation; it did not provide temporal, geographic, or domain-level external validation. No clinical implementation threshold was derived.

To avoid overclaiming, ROC-derived cut-offs, threshold-dependent sensitivity/specificity, calibration statistics, SHAP interpretation, and decision-curve results were not treated as evidence of clinical utility. Formal decision-curve analysis was removed from the main manuscript because the low event count and absence of external validation made clinical net-benefit claims inappropriate. We did not perform formal sample-size calculation for model development or external validation because this was a retrospective dataset assembled from available APP admissions; this limitation is explicitly considered in the Discussion. These conservative analytical and interpretive safeguards are summarized in **Table 3**.

*Ethical statement*

This retrospective study was conducted in strict accordance with the ethical guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of The First People's Hospital of Wuyi County. Due to the retrospective nature with de-identified clinical data, the requirement for written informed consent was waived by the ethics committee.

## Results

*Baseline characteristics*

A total of 127 APP patients were analyzed, including 110 survivors and 17 non-survivors. Baseline analysis showed that non-survivors had higher lymphocyte count, prothrombin-related abnormalities, D-dimer, AST, creatinine, and glucose levels, but lower neutrophil percentage, SIRI, NLR, RBC, hemoglobin, and albumin. The between-group comparison for SIRI was significant using the two-sided test reported in **Table 1** ($P = 0.042$). These findings suggest that fatal APP was characterized by inflammatory dysregulation, coagulation dysfunction, anemia or impaired oxygen-carrying capacity, and organ injury. However, due to the retrospective design and heterogeneous pesticide types, these associations should not be interpreted as causal evidence.

*Univariate logistic regression analysis*

Univariate logistic regression analysis was performed using two-sided tests to identify potential prognostic factors for mortality in APP. As shown in **Table 2**, SIRI, NLR, LMR, RBC, HGB,

**Table 3.** Conservative interpretation of exploratory internal machine-learning analyses

| Issue | Revised handling |
|---|---|
| Low event count | Only 17 deaths; all regression and ML results are exploratory. |
| Internal hold-out set | 70:30 split used only for internal checking, not external validation. |
| Threshold metrics | ROC cut-offs, sensitivity, specificity, and Youden index were not used clinically. |
| Calibration/utility | Calibration and DCA were not used to claim clinical usefulness. |
| SHAP | Model explanation only; not mechanistic evidence. |

Note: This table replaces unstable threshold-dependent performance claims with a conservative interpretation framework. Abbreviations: ML, machine learning; ROC, receiver operating characteristic; DCA, decision-curve analysis; SHAP, Shapley additive explanations.

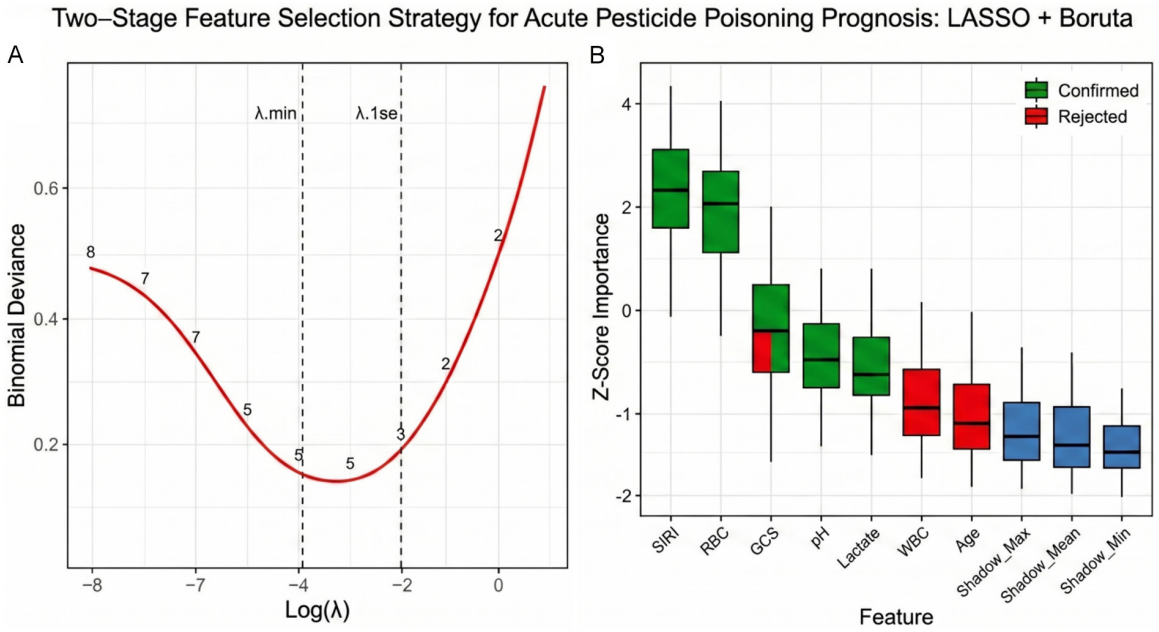


**Figure 2.** Feature selection for APP prognosis using LASSO and Boruta. A. LASSO cross-validation curve showing binomial deviance versus log(lambda); the lambda.1se criterion was selected for a sparse and stable variable subset. B. Boruta variable-importance boxplot showing Z-score importance. Green indicates confirmed predictors, red indicates rejected predictors, and blue indicates tentative or shadow features. The analysis was performed in the training set only.

D-dimer, APTT, AST, creatinine, glucose, albumin, and several leukocyte-related parameters were associated with mortality. The OR for SIRI was 0.82 (95% CI: 0.68-0.99, P = 0.042), indicating that higher SIRI was associated with lower mortality risk. This direction was consistent with the lower SIRI values in non-survivors shown in **Table 1**.

*Feature selection, multivariable adjustment, and dimensionality reduction*

To balance model interpretability and overfitting risk, we used a combined feature-selection strategy involving LASSO regression, the Boruta algorithm, and VIF-based collinearity screening. The LASSO and Boruta feature-selection results are shown in **Figure 2**. In addition, multivariable logistic regression was performed to evaluate whether SIRI retained an association with mortality after adjustment for clinically relevant confounders. As shown in **Table 4**, after adjustment for RBC, D-dimer, APTT, AST, creatinine, glucose, albumin, and pesticide type, lower SIRI remained associated with mortality (adjusted OR = 0.86, 95% CI: 0.74-0.99, P = 0.041). RBC also showed an association with lower mortality risk (adjusted OR = 0.18, 95% CI: 0.06-0.55, P = 0.003). Because only 17 deaths occurred, these adjust-

**Table 4.** Multivariable logistic regression analysis for mortality in APP

| Variable | Adjusted OR | 95% CI Lower | 95% CI Upper | *P*-value |
|---|---|---|---|---|
| SIRI | 0.86 | 0.74 | 0.99 | 0.041 |
| RBC ($\times 10^{12}$/L) | 0.18 | 0.06 | 0.55 | 0.003 |
| D-Dimer (per 1000 μg/L) | 1.08 | 1.01 | 1.17 | 0.028 |
| APTT (s) | 1.09 | 1.01 | 1.18 | 0.035 |
| AST (U/L) | 1.01 | 1.00 | 1.02 | 0.046 |
| Creatinine (μmol/L) | 1.02 | 1.00 | 1.05 | 0.049 |
| Albumin (g/L) | 0.87 | 0.75 | 0.99 | 0.044 |
| Non-organophosphate pesticide | 2.41 | 1.02 | 6.88 | 0.047 |

Note: Variables were selected according to clinical relevance, univariate candidate associations, and collinearity screening (VIF < 5). Because only 17 death events occurred, this model is exploratory, vulnerable to overfitting and coefficient instability, and should not be overinterpreted as definitive independent or externally validated evidence. Abbreviations: APP, acute pesticide poisoning; OR, odds ratio; CI, confidence interval; SIRI, systemic inflammatory response index; RBC, red blood cell count; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; VIF, variance inflation factor.

ed results should be interpreted as exploratory associations that are vulnerable to overfitting and coefficient instability, not as definitive independent prognostic effects.

Given the limited event count, the selected predictors should be viewed as candidate variables that may be sensitive to resampling, case-mix composition, and the proportion of non-organophosphate exposures. In particular, the apparent RBC-SIRI pattern should be tested in larger cohorts before being used as a stable prognostic signature.

*SIRI dynamics across prognostic subgroups and its correlation with canonical inflammatory markers*

SIRI differed across prognostic categories in APP. The recovery group showed higher median values and greater dispersion, whereas the death group showed consistently lower levels, supporting the candidate value of SIRI as an exploratory prognostic marker (**Figure 3A**). For pesticide categories, herbicide cases showed higher and more dispersed SIRI values than organophosphate or rodenticide cases (**Figure 3B**). This comparison was exploratory and was not adjusted for poisoning dose, exposure route, time from exposure to admission, or treatment delay; therefore, it indicates statistical association rather than a pesticide-specific causal mechanism.

The pesticide-category comparison was retained to address toxicant heterogeneity, but the number of non-organophosphate cases was small. Therefore, the higher dispersion of SIRI in herbicide-related cases should be interpreted as a signal of heterogeneity requiring focused validation, not as evidence that SIRI has a uniform mechanism or threshold across pesticide categories.

*Model construction and evaluation*

To explore nonlinear variable patterns without presenting a clinically validated prediction model, the dataset was randomly divided into a training set (70%, n = 89) and an internal hold-out set (30%, n = 38) using stratified sampling to preserve the survival/non-survival ratio. Within the training set, repeated 10-fold cross-validation and grid search were used for hyperparameter optimization. The LR model used L2 regularization; the RF model used 500 trees, square-root feature selection at each split, and class weighting; and the SVM model used a radial basis function kernel with grid-searched C (0.1, 1, 10) and sigma (0.01, 0.05, 0.1). No hold-out-set information was used during hyperparameter tuning. Because the hold-out set contained very few fatal events, threshold-dependent sensitivity/specificity, ROC cut-off points, and calibration tests were not used as model-selection or clinical-implementation criteria. The complete model-development and internal-evaluation settings are summarized in **Table 5**.

*Integrating hematological and inflammatory indicators: SHAP-based interpretation of the exploratory model*

Exploratory Spearman correlations between SIRI and traditional peripheral blood parameters are shown in **Figure 4**. SHAP analysis of the SVM-based exploratory framework (**Figure 5**) showed that RBC, HGB, hs-CRP, PDW, RDW, GLU, NLR, fibrinogen, lymphocyte percentage, albumin, AST, ALT, APTT, and monocyte count contributed to model output. Although hs-CRP was not significant in univariate analysis, it may

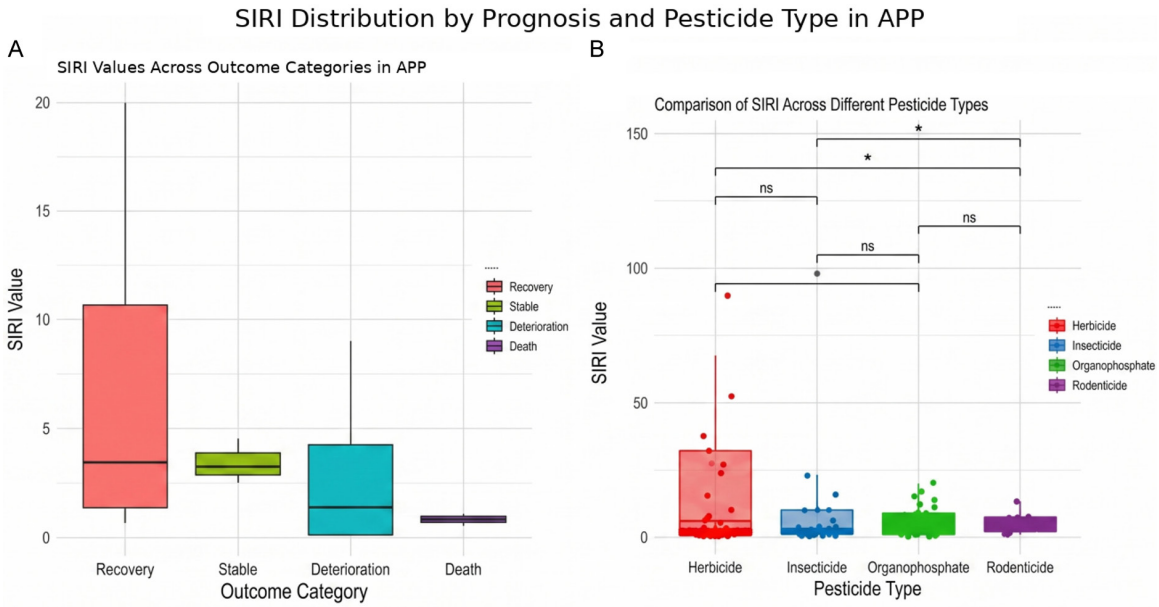


**Figure 3.** Distribution of SIRI values by prognosis and pesticide type. A. SIRI values across outcome categories in APP patients. B. Exploratory four-category comparison of SIRI values across recorded pesticide types. Data are shown as boxplots with jittered individual observations; the y-axis represents SIRI calculated as neutrophil count × monocyte count/lymphocyte count. Two-sided Kruskal-Wallis tests with post hoc pairwise comparisons were used. $^{*}P < 0.05$, $^{**}P < 0.01$, ns = not significant. Because non-organophosphate subgroups were sparse, pesticide-category differences should be interpreted as exploratory only.

**Table 5.** Transparent reporting of exploratory machine learning model development and internal evaluation

| Item | Reported setting |
|---|---|
| Data split | 70:30 stratified split: training n = 89; internal hold-out n = 38. The hold-out set was not an external validation cohort. |
| Class imbalance | Class weights in RF/SVM; minority class weighted inversely to frequency. |
| Cross-validation | Repeated 10-fold CV within training set only. |
| Hyperparameter search | SVM: RBF, C 0.1/1/10, sigma 0.01/0.05/0.1; RF: 500 trees, mtry=sqrt(p); LR: L2. |
| Calibration | Formal calibration curves and calibration-based model selection were not emphasized because of small hold-out n and few fatal events; H-L results, if calculated, were interpreted only as descriptive. |
| External validation | Not performed; temporal, geographic, domain-level, and multicenter validation are required before clinical use. |
| Event count | Only 17 deaths occurred in the full cohort; multivariable regression, variable selection, and ML metrics are statistically unstable and exploratory. |
| Clinical use | No clinical decision threshold was recommended. ROC-derived cut-offs and decision-curve results were not used to support implementation before independent external validation and calibration updating. |

Abbreviations: ML, machine learning; RF, random forest; SVM, support vector machine; CV, cross-validation; RBF, radial basis function; LR, logistic regression; H-L, Hosmer-Lemeshow; ROC, receiver operating characteristic.

provide auxiliary information through nonlinear interactions with hematological, coagulation, and organ-function indicators. This should not be interpreted as independent prognostic value of hs-CRP. More importantly, SHAP explains how variables influenced the fitted model; it does not establish biological mechanisms. Overall, the SHAP results support the view that mortality prediction in APP may depend on the combined pattern of oxygen-carrying capacity, inflammatory dysregulation, coagulation disturbance, and organ injury rather than on a single

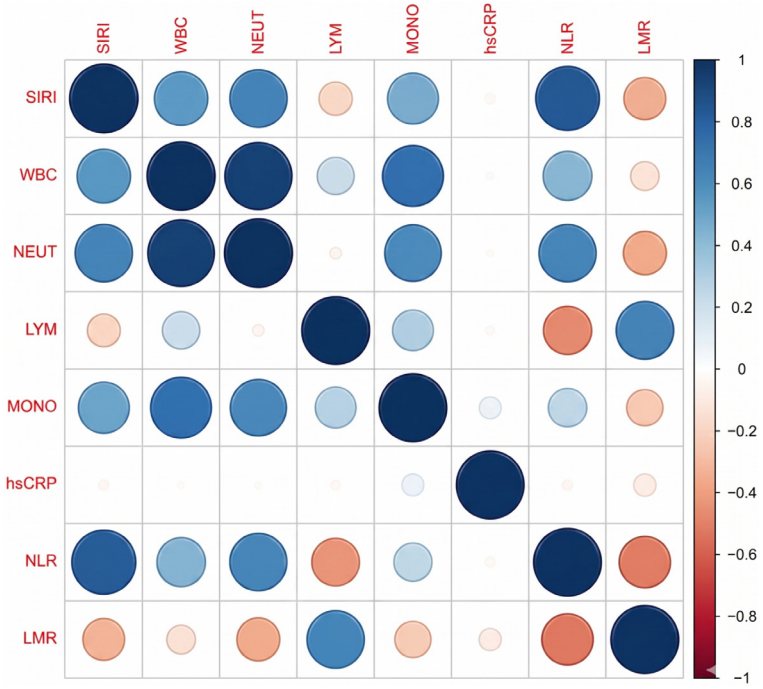


**Figure 4.** Correlation between SIRI and traditional peripheral blood parameters. Correlations were assessed using Spearman correlation analysis in the full cohort (n = 127). The size of each circle represents the absolute correlation coefficient, and the color represents the direction and magnitude of correlation, with blue indicating positive correlation and red indicating negative correlation. Variables included SIRI, WBC, NEUT, LYM, MONO, hs-CRP, NLR, and LMR. This heatmap was used for exploratory correlation visualization and was not used as independent evidence of causality.

marker alone, but this interpretation remains exploratory.

Threshold-dependent ROC cut-offs and decision-curve analysis were not retained as clinical evidence because the hold-out set contained very few non-survivors and no independent external validation was available. Consequently, the SVM analysis should be viewed only as an exploratory fitted framework for variable-ranking and hypothesis generation. Prospective multicenter validation with adequate fatal events, prespecified calibration assessment, and decision-impact analysis would be required before any model-derived threshold could be considered for routine use.

## Discussion

Acute pesticide poisoning (APP) is caused by exposure to toxic agricultural chemicals, including organophosphates, herbicides, insecticides, and rodenticides. It remains an important emergency condition in agricultural regions and is associated with respiratory failure, circulatory instability, coagulation abnormalities, and multi-organ injury [15]. Existing studies have mainly focused on toxicological mechanisms and emergency treatment, whereas risk prediction using routinely available inflammatory and hematological markers remains insufficiently developed. In this study, we evaluated SIRI together with machine learning models to explore early prognostic stratification in APP.

Recent clinical studies further support the need to distinguish pesticide categories when interpreting inflammatory or machine learning results. For example, diquat poisoning cohorts emphasize renal injury, circulatory or neurologic deterioration, and toxicant-specific exposure information as major prognostic features [16, 17]. In contrast, aluminum phosphide poisoning studies have reported high NLR and PLR as mortality-associated inflammatory indices [18, 19], a direction that differs from the low-SIRI signal observed in the present mixed APP cohort. These differences indicate that peripheral blood indices may capture different toxic-inflammatory states depending on the compound, exposure dose, timing of sampling, and organ injury pattern [20].

Non-survivors showed obvious systemic dysfunction, including coagulation disturbance, increased D-dimer, prolonged APTT, liver and renal injury, and reduced RBC and hemoglobin. These abnormalities suggest that fatal APP is not simply an inflammatory disorder but a combined syndrome involving immune dysregulation, coagulation activation, impaired oxygen delivery, and organ damage. The SVM model was retained only as an exploratory nonlinear framework because support vector machines can capture complex interactions in small clinical datasets [21], but the present event count was too low to support stable performance claims. Therefore, the machine learning results

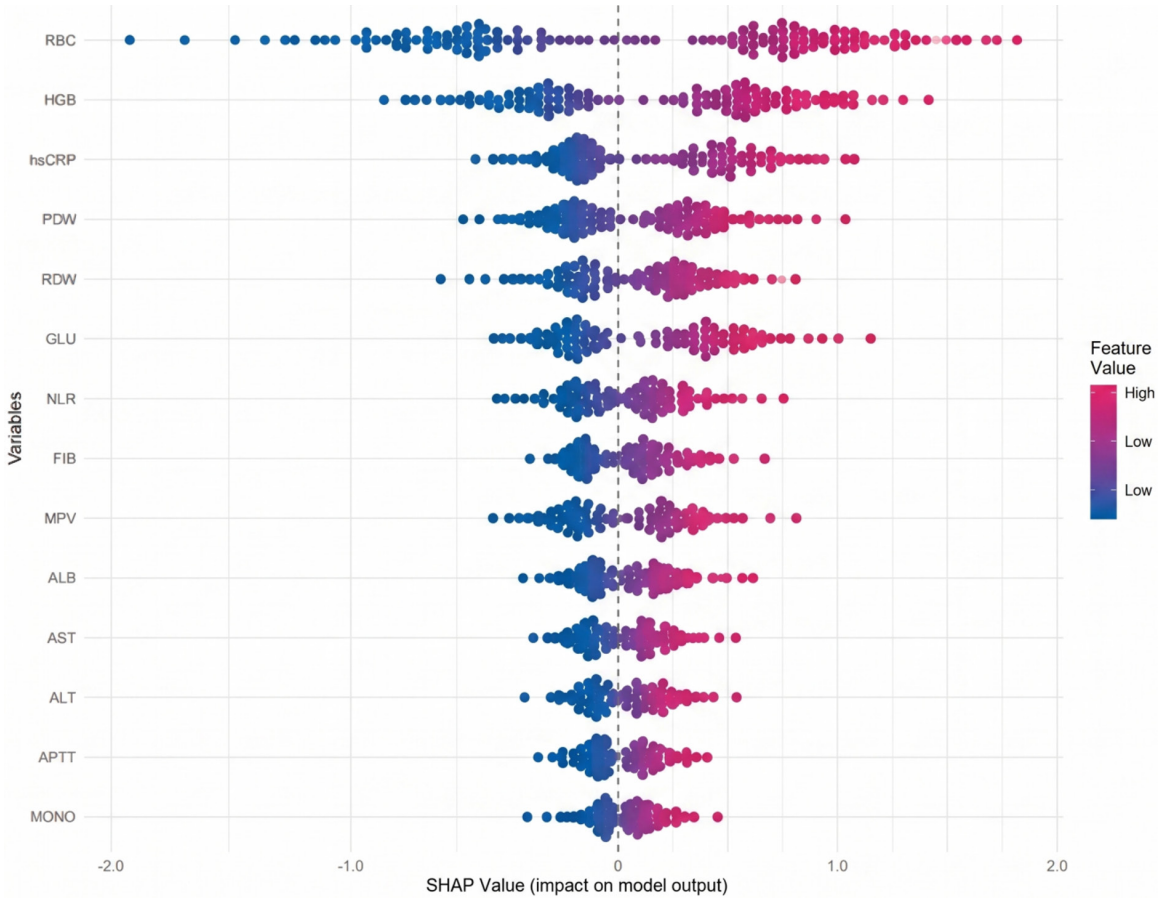


**Figure 5.** SHAP summary plot of clinical variables for the SVM-based exploratory predictive model. The x-axis represents SHAP value, indicating each variable's impact on model output; the y-axis lists variables ranked by mean absolute SHAP value. Dot color denotes feature value from low to high. SHAP analysis was performed to support model interpretation only and should not be regarded as mechanistic evidence of toxin-induced inflammatory pathways.

should be regarded as hypothesis-generating internal findings rather than validated prediction evidence.

The finding of lower SIRI in non-survivors should therefore not be interpreted as evidence that fatal APP is a low-inflammatory state. In this dataset, low SIRI may have reflected the mathematical combination of lower neutrophil-related indices, lower monocyte contribution, and relatively higher lymphocyte counts in a small number of fatal cases. Alternative explanations include toxin-specific leukocyte redistribution, delayed presentation, pre-hospital treatment, bone marrow or immune-cell exhaustion, dilutional or hemoconcentration effects, and organ-failure-related immune dysregulation. Because cytokines, lymphocyte subsets, neutrophil function, monocyte phenotypes, cholinesterase dynamics, paraquat/diquat concentrations, oxidative stress markers, and serial immune-cell measurements were not available, these mechanistic interpretations remain hypotheses that require prospective biological validation.

This study has several limitations. First, it was a single-center retrospective study with a total sample size of 127 patients and only 17 deaths, which substantially increases the risk of selection bias, model instability, unstable regression coefficients, and overly optimistic internal performance estimates. Second, no temporal, geographic, or independent external validation cohort was available; therefore, the model cannot yet be generalized to other hospitals, regions, treatment protocols, or pesticide exposure patterns. Third, APP included mixed pesticide types, and the dose, exposure route, treatment delay, blood sampling time, pre-hospital interventions, and specific toxicant concentrations were incompletely recorded, which may

introduce residual confounding and limit interpretation of pesticide-category differences. Fourth, missing data were handled by complete-case screening for key variables and limited median imputation for low-missingness variables, but more rigorous prospective data collection is needed. Fifth, mechanistic indicators such as cytokine profiles, lymphocyte subsets, neutrophil function, monocyte phenotypes, cholinesterase activity dynamics, and oxidative stress markers were not measured; therefore, the proposed immune-dysregulation explanation for low SIRI remains a biological hypothesis rather than direct mechanistic evidence. Sixth, although the SVM model showed favorable internal performance, the small number of events limits hyperparameter stability, SHAP interpretation, calibration assessment, and subgroup analysis. Future multicenter prospective studies should include predefined sample-size estimation, standardized exposure and sampling-time records, pesticide-category-stratified analyses, measured inflammatory and immune-cell biomarkers, external validation, calibration updating, and clinical impact assessment before clinical implementation.

In summary, this revised analysis supports low SIRI as a candidate blood-count-derived prognostic signal in APP, but not as a mechanistically proven biomarker or an externally validated decision rule. The RBC-SIRI-based modelling pattern should be regarded as hypothesis-generating and requires larger, biologically annotated, pesticide-category-stratified, multicenter validation cohorts before it can be considered for clinical use.

## Disclosure of conflict of interest

None.

## Abbreviations

APP, Acute pesticide poisoning; SIRI, Systemic inflammatory response index; NEUT, Neutrophils; LYM, Lymphocytes; MONO, Monocytes; WBC, White blood cell count; NLR, Neutrophil-lymphocyte ratio; RBC, Red blood cell count; HGB, Hemoglobin; APTT, Activated partial thromboplastin time; D-D, D-dimer; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; GLU, Glucose; PDW, Platelet distribution width; RDW, Red cell distribution width; FIB, Fibrinogen; MPV, Mean platelet volume; Cr, Creatinine; hs-CRP, High-sensitivity C-reactive protein; RF, Random forest; SVM, Support vector machine; AUC, Area under the receiver operating characteristic curve; 10-fold CV, 10-fold cross-validation.

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