

Inflammatory Profile in Acute Ischemic Stroke with significance in carotid artery metabolism : Associations with Alcohol Consumption, Neurological Severity, and Functional Status in view of One Health

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Abstract

Background

Acute ischemic stroke (AIS) is characterized by substantial biological and clinical heterogeneity, in which systemic inflammation, neurological impairment, cardiovascular risk, carotid artery metabolism dysregulation and lifestyle-related factors may contribute differently to the overall phenotype. This study investigated the inflammatory profile of patients with AIS and its relationships with neurological-functional severity and documented alcohol status.

Methods

A retrospective observational study included 71 patients with acute ischemic cerebrovascular events treated in a neurological department in Romania. Systemic inflammatory and biological status was assessed using C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, and hemoglobin (HGB), while neurological and functional status was characterized using the National Institutes of Health Stroke Scale (NIHSS), modified Rankin Scale (mRS), and Gugging Swallowing Screen (GUSS). Principal component analysis (PCA) and categorical principal component analysis (CATPCA) were used to identify latent biological-clinical structures. Patients were subsequently compared according to documented alcohol status using non-parametric analysis, and the association with log-transformed CRP was examined using unadjusted and multivariable linear regression.

Results

Biological PCA identified a single systemic inflammatory-biological component dominated by ESR and fibrinogen, explaining 56.1% of biological variance. Incorporation of NIHSS, mRS, and GUSS produced a two-component solution explaining 71.1% of total variance and distinguished a neurological-functional severity component from an inflammatory-biological component. CATPCA extended this structure to the broader patient profile, identifying an Inflammatory-Neurological Severity Dimension and an Age-Cardiovascular Profile Dimension. Documented alcohol status contributed only modestly to these latent dimensions, indicating that it was not a major determinant of the overall multidimensional phenotype. Targeted comparison nevertheless identified CRP as the only investigated biological or clinical variable differing significantly between alcohol-status categories (Mann–Whitney $U = 293.5$, $p = 0.026$). The alcohol-status coefficient remained significant after adjustment for age, sex, obesity, and metabolic disease ($B = 0.732$, 95% CI $0.071–1.394$, $p = 0.031$), although the adjusted model had limited explanatory capacity ($R^2 = 0.086$) and was not statistically significant overall ($p = 0.307$).

Conclusions

AIS was characterized by related but distinguishable inflammatory-biological and neurological-functional domains embedded within a broader multidimensional clinical phenotype. Documented alcohol status did not define this global structure but showed a selective association with CRP that persisted after adjustment for selected demographic and metabolic factors. These findings suggest that alcohol-related characteristics may be linked to a specific component of systemic inflammatory activity rather than to generalized inflammation or greater neurological-functional severity. Prospective studies with quantitative assessment of alcohol exposure and longitudinal inflammatory profiling are required to confirm this association.

1. Introduction

Acute ischemic stroke (AIS) remains a major cause of mortality, disability, and long-term functional dependence worldwide and represents the predominant form of cerebrovascular disease, accounting for approximately 70–80% of cerebrovascular events [1]. Despite considerable advances in acute stroke management, including intravenous thrombolysis, mechanical thrombectomy, and increasingly standardized neurovascular care pathways, the clinical evolution of AIS remains heterogeneous [2,3]. This variability reflects not only differences in the location and extent of cerebral ischemia, but also the interaction between vascular risk factors, cardiovascular and metabolic comorbidities, systemic biological responses, and individual patient characteristics [4–8]

Inflammation has emerged as a central mechanism in the pathophysiology of cerebral ischemia and atherosclerotic vascular disease. At the level of the atherosclerotic plaque, macrophages, T and B lymphocytes, and natural killer cells participate in a complex inflammatory microenvironment that contributes to plaque progression and instability especially at the carotid artery level [9]. Following cerebral ischemia, tissue injury initiates additional inflammatory processes involving endothelial activation, immune-cell recruitment, blood-brain barrier dysfunction, and amplification of local and systemic inflammatory signaling. These mechanisms support the concept that AIS should be understood not only as an acute vascular occlusive event but also as a dynamic neurovascular and systemic inflammatory condition [6,9–11].

Circulating inflammatory biomarkers may therefore provide clinically accessible information regarding the biological response accompanying AIS. C-reactive protein (CRP) is widely used as a marker of systemic inflammation and has also been implicated in processes related to vascular inflammation and blood-brain barrier dysfunction [11]. Other inflammatory mediators, including cytokines and composite hematological indices, have been investigated in relation to neurological injury and neuroinflammatory responses [1,10,11]. Because individual inflammatory markers represent different biological pathways, their combined assessment may provide a more comprehensive characterization of the inflammatory state than the interpretation of a single biomarker in isolation.

Fibrinogen is particularly relevant in ischemic vascular disease because it represents an important interface between inflammation and coagulation. As an acute-phase protein and major determinant of

blood coagulation, elevated fibrinogen may characterize a biological environment involving both inflammatory activation and enhanced thrombotic potential. Erythrocyte sedimentation rate (ESR), although substantially less specific, may provide complementary information regarding systemic inflammatory activity. Consequently, the simultaneous evaluation of CRP, fibrinogen, and ESR may capture different but interconnected components of the inflammatory profile accompanying cerebral ischemia. The original clinical framework of the present study also emphasized considerable interindividual variability in CRP, fibrinogen, and ESR values, supporting their collective evaluation in relation to cerebrovascular disease rather than their interpretation as isolated laboratory measurements [5].

The biological response to ischemic stroke may also be clinically relevant to neurological severity and functional impairment. The National Institutes of Health Stroke Scale (NIHSS) is routinely used to quantify neurological deficits in patients with acute stroke, while the modified Rankin Scale (mRS) provides a measure of disability and functional dependence. The Gugging Swallowing Screen (GUSS) further contributes to the clinical characterization of stroke-related functional impairment by assessing swallowing dysfunction and aspiration risk. Previous research has increasingly supported an integrated approach to AIS in which neurological severity, vascular risk factors, biological mechanisms, and post-stroke functional status are evaluated together rather than as independent domains [4,12–14].

Lifestyle-related exposures represent another potentially relevant component of this multidimensional framework. Smoking, sedentary behavior, dietary factors, and alcohol consumption may interact with established cardiovascular and metabolic risk factors and can influence vascular biology over time [4,15]. Alcohol exposure is particularly complex because its biological effects may depend on the amount, duration, and pattern of consumption, while retrospective clinical records frequently provide only categorical information regarding alcohol status. Furthermore, alcohol exposure may coexist with hypertension, dyslipidemia, obesity, metabolic disease, cardiovascular disease, and other determinants of cerebrovascular risk. Consequently, associations between alcohol status and inflammatory activity in AIS should be interpreted within the broader clinical profile of the patient rather than as isolated causal effects [16–18].

The relationship between alcohol exposure and acute neurological presentations may be further complicated by underreporting or incomplete characterization in routine clinical practice. The original clinical material emphasizes that alcohol consumption may not always be fully acknowledged by patients or relatives, which can limit the precision of retrospective exposure classification. Moreover, alcohol-related neurological manifestations may overlap with other acute neuropsychiatric or metabolic conditions. For these reasons, analyses based on retrospective hospital datasets should distinguish clearly between documented alcohol status and more specific diagnoses such as chronic alcohol dependence or alcohol-related disorders [19–22].

Although inflammation, vascular risk factors, neurological severity, and functional outcome have each been extensively investigated in AIS, fewer studies have examined these domains simultaneously within

a single real-world clinical cohort. In particular, there remains a need for exploratory studies assessing whether routinely available inflammatory biomarkers form a coherent biological profile associated with neurological and functional severity, while also examining how documented alcohol status relates to this inflammatory phenotype.

A further gap concerns the analytical integration of heterogeneous clinical information. Traditional univariate analyses can identify differences in individual biomarkers but may not adequately capture the multidimensional relationships among inflammation, neurological severity, functional impairment, cardiovascular risk factors, and lifestyle-related exposures. Dimension-reduction approaches may therefore complement conventional comparisons by identifying latent clinical-biological structures within relatively small observational datasets.

Within this context, the relationship between documented alcohol consumption and systemic inflammatory activity in AIS deserves particular attention. The available literature and the original clinical framework recognize alcohol as a potentially relevant lifestyle-related factor, but the extent to which alcohol status is associated with inflammatory biomarkers independently of demographic and metabolic characteristics remains insufficiently characterized in routine-care cohorts.

The primary aim of this study was to characterize the inflammatory profile of patients with acute ischemic stroke and to investigate its associations with documented alcohol consumption, neurological severity, and functional status. The study pursued the following objectives:

- O1. To describe the demographic, cardiovascular, metabolic, neurological, therapeutic, and biological characteristics of the study cohort.
- O2. To characterize systemic inflammatory status using CRP, ESR, fibrinogen, and hemoglobin.
- O3. To investigate the relationships between inflammatory biomarkers and neurological and functional measures, including NIHSS, mRS, and GUSS.
- O4. To identify underlying multidimensional clinical-biological patterns using principal component analysis and categorical principal component analysis.
- O5. To compare inflammatory biomarkers and clinical severity measures between patients according to documented alcohol status.
- O6. To determine whether the association between alcohol status and CRP persists after adjustment for selected demographic and metabolic covariates.
- O7. To explore the contribution of cardiovascular and metabolic comorbidities to the multidimensional clinical profile of patients with AIS.

Accordingly, the study addressed the following research questions:

RQ1. What inflammatory profile characterizes patients with acute ischemic stroke in the investigated cohort?

RQ2. Are CRP, ESR, fibrinogen, and hemoglobin associated with neurological severity and functional status as assessed by NIHSS, mRS, and GUSS?

RQ3. Can inflammatory and clinical variables be reduced to interpretable multidimensional components reflecting distinct biological and neurological patterns?

RQ4. Do patients with different documented alcohol-status categories differ in their inflammatory biomarker profiles?

RQ5. Is documented alcohol status associated with CRP independently of age, sex, obesity, and metabolic disease?

RQ6. How do demographic characteristics, cardiovascular comorbidities, metabolic disease, and thrombolytic treatment contribute to the broader multidimensional profile of AIS?

The novelty of the present study lies in the integrated analysis of routinely available inflammatory biomarkers, documented alcohol status, neurological severity, and functional status within the same AIS cohort. Rather than considering CRP, ESR, and fibrinogen exclusively as isolated laboratory markers, the study evaluates their joint contribution to a broader inflammatory phenotype and examines their relationship with NIHSS, mRS, and GUSS. In addition, conventional group comparisons are complemented by PCA and CATPCA in order to explore latent clinical-biological dimensions within the cohort. A further contribution is the assessment of the alcohol-CRP relationship using both unadjusted and multivariable analyses, thereby distinguishing a simple between-group difference from an association evaluated after accounting for selected demographic and metabolic covariates.

Following this Introduction, Section 2, Materials and Methods, describes the retrospective observational design, study population, variables, biomarker assessment, clinical scales, and statistical procedures. Section 3, Results, presents the descriptive characteristics of the cohort, the inflammatory and clinical profiles, the PCA and CATPCA findings, the comparison according to alcohol status, and the adjusted analysis of CRP. Section 4, Discussion, interprets the findings in relation to the existing literature, addresses their clinical implications, and discusses the methodological limitations of the study. Finally, Section 5, Conclusions, summarizes the principal findings and outlines their relevance for the integrated clinical assessment of patients with acute ischemic stroke.

2. Materials and Methods

2.1. Study Design and Setting

A retrospective observational study was conducted using clinical data from patients evaluated and treated in the Neurology Department of the Emergency Clinical County Hospital of Brăila, Romania. Data

were retrieved retrospectively from hospital medical records during the first six months of 2025. The study was designed to investigate the inflammatory profile of patients with acute ischemic stroke and its relationships with documented alcohol status, neurological severity, and functional status.

The analytical database was structured into demographic, cardiovascular, neurological, metabolic, inflammatory, therapeutic, lifestyle-related, and clinical severity domains. Variable definitions and coding are summarized in Table 1.

Table 1
Variables included in the analytical dataset

Analytical domain	Variable	Definition	Measurement / coding	Role in the analysis
Demographic characteristics	SEX	Biological sex	1 = Female; 2 = Male	Descriptive analysis; CATPCA; adjusted regression
	AGE	Age category	1 = < 50; 2 = 50–59; 3 = 60–69; 4 = 70–79; 5 = ≥ 80 years	Descriptive analysis; CATPCA; alcohol-group comparison; adjusted regression
	URBAN	Area of residence	1 = Urban; 2 = Rural	Descriptive analysis; CATPCA
Cardiovascular profile	HTACardiacD	Arterial hypertension	1 = No; 2 = Yes	CATPCA
	FIACardiacD	Atrial fibrillation	1 = No; 2 = Yes	CATPCA
	IHD	Ischemic heart disease	1 = No; 2 = Yes	CATPCA
Metabolic profile	METAB_DISEASE	Metabolic disease	1 = No; 2 = Yes	CATPCA; adjusted regression
	DYSLIP_MIXED	Mixed dyslipidemia	1 = No; 2 = Yes	CATPCA
	OBESITY	Obesity	1 = No; 2 = Yes	CATPCA; adjusted regression
Stroke-related treatment	AISTHROMB	Acute ischemic stroke treated with thrombolysis	1 = No; 2 = Yes	CATPCA
Lifestyle exposure	ALCOHOL	Documented alcohol status	1 = No; 2 = Yes	Main grouping/exposure variable; CATPCA; Mann-Whitney analysis; regression
Biological and inflammatory profile	HGB	Hemoglobin	Continuous, g/dL	PCA; CATPCA; alcohol-group comparison
	ESR	Erythrocyte sedimentation	Continuous, mm/h	PCA; CATPCA; alcohol-group

Note: Binary variables were coded as 1 = No and 2 = Yes. Age was available as an ordinal five-category variable. HGB, ESR, fibrinogen, and CRP were analyzed in their original quantitative form. For the multivariable analysis, CRP was additionally transformed using its natural logarithm (LN_CRP) to improve distributional properties. Temporary transformations required by specific CATPCA procedures and PCA-derived component scores were analytical variables and were not part of the original clinical database.

Analytical domain	Variable	Definition	Measurement / coding	Role in the analysis
		rate		comparison
	FIBRINOGEN	Plasma fibrinogen	Continuous, mg/dL	PCA; CATPCA; alcohol-group comparison
	CRP	C-reactive protein	Continuous, original laboratory value	PCA; CATPCA; alcohol-group comparison; regression
Neurological severity	NIHSS	National Institutes of Health Stroke Scale	Clinical severity score	PCA; CATPCA; alcohol-group comparison
Functional status	MRS	Modified Rankin Scale	Ordinal score, 0–6	PCA; CATPCA; alcohol-group comparison
	GUSS	Gugging Swallowing Screen	Ordinal clinical score	PCA; CATPCA; alcohol-group comparison
<p><i>Note: Binary variables were coded as 1 = No and 2 = Yes. Age was available as an ordinal five-category variable. HGB, ESR, fibrinogen, and CRP were analyzed in their original quantitative form. For the multivariable analysis, CRP was additionally transformed using its natural logarithm (LN_CRP) to improve distributional properties. Temporary transformations required by specific CATPCA procedures and PCA-derived component scores were analytical variables and were not part of the original clinical database.</i></p>				

Source Authors' Contributions

Clinical, demographic, biological, cardiovascular, metabolic, lifestyle-related, and neurological information available during the index hospitalization was extracted and entered into an anonymized research database. No additional investigations or interventions were performed for research purposes, and all analyses were based exclusively on information recorded during routine clinical care. Variables retained in the final analytical dataset were selected according to the predefined study objectives and the subsequent univariate and multivariate analytical framework; their operational definitions are presented in Table 1.

2.2. Study Population and Eligibility Criteria

The study cohort comprised adult patients hospitalized with acute ischemic cerebrovascular events during the predefined study period. Patients were eligible when an ischemic neurological event had been clinically established and sufficient clinical and laboratory information was available for inclusion in the analytical database.

Inclusion criteria comprised age ≥ 18 years, a diagnosis of acute ischemic cerebrovascular disease, availability of neurological assessment, and availability of the principal biological parameters required for the study. Both thrombolysed and non-thrombolysed patients were eligible, allowing the cohort to reflect the clinical heterogeneity encountered in routine neurological practice.

Patients presenting with primary hemorrhagic neurological conditions were excluded. Exclusion criteria comprised intracerebral hemorrhage, subarachnoid hemorrhage of traumatic or non-traumatic origin, intraventricular hemorrhage, and other primary hemorrhagic cerebral lesions. Patients presenting with conditions potentially mimicking an ischemic cerebrovascular event, including uncomplicated migraine, migraine with aura, paresthesia related to tetany, isolated vertiginous syndromes, cerebral abscesses, and selected cerebral malformations, were also excluded. Patients who were comatose at presentation were not included.

2.3. Data Collection and Study Variables

Data extraction covered demographic characteristics, vascular and metabolic comorbidities, neurological history, inflammatory and hematological parameters, stroke-related characteristics, selected treatments, lifestyle-related exposures, and clinical severity measures.

Demographic variables included sex, age category, and urban or rural residence. Age was available in predefined categories rather than as a continuous variable. Cardiovascular and vascular characteristics included arterial hypertension, atrial fibrillation, ischemic heart disease, heart failure, dyslipidemia-related conditions, previous myocardial infarction, and obesity. Metabolic disease and relevant chronic neurological comorbidities were also recorded.

Stroke-related variables included transient ischemic attack, thrombolysed acute ischemic stroke, and non-thrombolysed acute ischemic stroke. Treatment variables included major classes of antihypertensive, antiplatelet, anticoagulant, and lipid-lowering medication when available in the medical record.

Documented alcohol status was treated as a categorical exposure derived from the original clinical database, with 1 representing *no documented* alcohol consumption and 2 representing *documented* alcohol consumption. Chronic alcoholism was recorded separately and was not used interchangeably with the alcohol-consumption variable.

The principal biological variables selected for analysis were hemoglobin (HGB), erythrocyte sedimentation rate (ESR), fibrinogen, and C-reactive protein (CRP). These parameters were selected because they were consistently available within the dataset and jointly represented hematological, inflammatory, and inflammation-coagulation dimensions relevant to the biological profile of acute ischemic stroke.

CRP, ESR, and fibrinogen were analyzed both individually and as components of a broader inflammatory profile. Hemoglobin was retained as a complementary biological variable because hematological

alterations may coexist with systemic inflammatory and vascular abnormalities.

No composite inflammatory score was imposed a priori. Instead, the latent structure of the biological variables was investigated empirically using dimension-reduction procedures.

Neurological severity was assessed using the National Institutes of Health Stroke Scale (NIHSS). Functional disability was characterized using the modified Rankin Scale (mRS), while swallowing-related functional impairment was evaluated using the Gugging Swallowing Screen (GUSS).

These variables were analyzed as separate clinical indicators and were subsequently incorporated into multivariate dimension-reduction analyses to investigate whether inflammatory and clinical characteristics clustered into interpretable biological-neurological patterns.

2.4. Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics. Categorical variables were summarized using absolute and relative frequencies, whereas continuous variables were characterized using measures of central tendency and dispersion according to their distribution. Distributional characteristics were evaluated using graphical inspection and tests of normality where appropriate. All statistical tests were two-sided, with a significance threshold of $p < 0.05$.

Principal component analysis (PCA) was used as an exploratory dimension-reduction procedure. An initial biological PCA included HGB, ESR, fibrinogen, and CRP to determine whether these markers could be represented by a smaller number of underlying components. A second, extended PCA incorporated the inflammatory and biological variables together with NIHSS, mRS, and GUSS in order to investigate the joint structure of biological inflammation, neurological severity, and functional impairment. Suitability of the correlation matrix for PCA was evaluated using the Kaiser-Meyer-Olkin measure of sampling adequacy and Bartlett's test of sphericity. Component retention was guided by eigenvalues greater than 1 together with inspection of the scree plot. When more than one component was retained, Varimax rotation was applied to facilitate interpretation of component loadings. Regression-based component scores were generated for subsequent exploratory analyses.

Categorical principal component analysis (CATPCA) was used as a complementary exploratory approach to account for the heterogeneous measurement properties of the dataset and to investigate broader multidimensional relationships that could not be adequately represented by conventional PCA alone. The extended CATPCA model incorporated demographic variables, selected cardiovascular and metabolic comorbidities, thrombolysis status, documented alcohol status, HGB, ESR, fibrinogen, CRP, and the clinical variables GUSS, mRS, and NIHSS. A two-dimensional solution was specified to obtain an interpretable representation of the principal clinical-biological structures within the cohort.

Variables with extremely limited variability, including chronic alcoholism documented in only a single case, were not used as defining variables in the principal multivariate model because they could not contribute reliably to dimension extraction.

PCA and CATPCA were therefore considered complementary rather than interchangeable analyses: conventional PCA was used to characterize the structure of the principal continuous biological and clinical measures, whereas CATPCA was used to explore the wider configuration of mixed clinical, categorical, and biological variables.

2.5. Analysis according to documented alcohol status

Patients were subsequently compared according to documented alcohol-consumption status. Because several inflammatory and clinical variables demonstrated non-normal or asymmetric distributions, between-group comparisons for HGB, ESR, fibrinogen, CRP, GUSS, mRS, and NIHSS were performed using the Mann-Whitney U test. Age-category distributions were examined separately to assess whether the two alcohol-status groups differed systematically with respect to age.

This analysis was intended to determine whether documented alcohol status was associated with differences in inflammatory or clinical characteristics without assuming normality of the underlying distributions.

2.6. Multivariable Analysis of CRP

Given the distributional characteristics of CRP, values were logarithmically transformed before regression modeling. The natural logarithm of CRP (LN_CRP) was used as the dependent variable.

Two linear regression models were specified. An unadjusted model evaluated the association between alcohol-consumption status and log-transformed CRP. A multivariable model subsequently adjusted this relationship for age, sex, obesity, and metabolic disease, selected as clinically relevant demographic and metabolic covariates available within the dataset.

Model assumptions were evaluated through examination of standardized residuals, histograms, and normal probability plots. Collinearity diagnostics, including tolerance and variance inflation measures, were examined in the adjusted model. Regression coefficients were reported with 95% confidence intervals.

2.7. Robustness and Sensitivity Assessment

Robustness of the principal alcohol-inflammation finding was evaluated through complementary analytical approaches rather than reliance on a single statistical procedure. Non-parametric comparison of CRP according to alcohol status was complemented by regression analysis using log-transformed CRP.

Consistency between the unadjusted and adjusted regression models was examined to determine whether the observed relationship remained after accounting for selected demographic and metabolic characteristics. The convergence of results obtained through non-parametric group comparison and multivariable modeling was considered when interpreting the stability of the observed association.

Dimension-reduction findings were likewise evaluated using both conventional PCA and CATPCA. This dual analytical strategy allowed the latent structure identified among the principal continuous clinical and biological variables to be compared with a broader model incorporating categorical clinical characteristics.

2.8. Missing Data

Analyses were conducted using available clinical information recorded in the database. Missing values were not replaced through external imputation procedures. Case inclusion therefore depended on the variables required for each specific analysis, and the corresponding SPSS procedure was used to handle unavailable observations according to the analytical model.

Original clinical coding was preserved in the master dataset, and any transformations required for statistical analysis were performed using derived variables without altering the source variables.

2.9. Ethical Considerations

The study was conducted retrospectively using anonymized clinical information collected during routine medical care. The research protocol received approval from the Ethics Committee of the Emergency Clinical County Hospital of Brăila, approval no. 36/05.12.2023.

Data were analyzed in anonymized form, and no information allowing direct identification of individual patients was included in the analytical dataset or manuscript.

3. Results

3.1. Biological and Clinical Multidimensional Structure

PCA restricted to HGB, ESR, fibrinogen, and CRP identified a single dominant component, supported by acceptable sampling adequacy ($KMO = 0.651$) and a significant Bartlett test ($\chi^2 = 81.498$, $df = 6$, $p < 0.001$). This component had an eigenvalue of 2.244 and explained 56.1% of total variance. ESR and fibrinogen showed the strongest loadings, at 0.899 and 0.864, respectively, followed by CRP (0.621) and HGB (0.550).

Given this loading pattern, the component was interpreted as a Systemic Inflammatory-Biological Component. Its structure indicates that the four biological markers were not distributed across several independent latent processes but converged on a common biological axis, dominated by ESR and fibrinogen. Communalities were highest for ESR and fibrinogen, whereas CRP and HGB were represented more modestly within the component.

Table 2 summarizes the transition from this single biological component to the broader biological-clinical PCA.

Table 2
Principal component structure and interpretation of the biological and extended biological-clinical models

Parameter	Biological PCA	Extended biological-clinical PCA
Variables included	HGB, ESR, fibrinogen, CRP	HGB, ESR, fibrinogen, CRP, NIHSS, mRS, GUSS
KMO	0.651	0.679
Bartlett χ^2	81.498	301.997
df	6	21
p	< 0.001	< 0.001
Components retained	1	2
Component 1 interpretation	Systemic Inflammatory-Biological Component	Neurological-Functional Severity Component
Eigenvalue, Component 1	2.244	3.099
Variance explained, Component 1	56.1%	44.3%
Component 2 interpretation	-	Inflammatory-Biological Component
Eigenvalue, Component 2	-	1.878
Variance explained, Component 2	-	26.8%
Cumulative variance	56.1%	71.1%

Source: Authors' calculations using IBM SPSS Statistics, version 26.

When NIHSS, mRS, and GUSS were added, the dimensional structure separated into two components. Sampling adequacy remained acceptable (KMO = 0.679), and Bartlett's test remained significant ($\chi^2 = 301.997$, $df = 21$, $p < 0.001$). Two components with eigenvalues of 3.099 and 1.878 jointly explained 71.1% of the total variance. The first component was dominated by NIHSS, mRS, and GUSS, with nearly identical loadings of 0.848, 0.847, and 0.847. It was therefore interpreted as the Neurological-Functional Severity Component. This convergence indicates that neurological deficit, disability, and swallowing-related functional impairment represented a common clinical severity construct within the cohort. The second component was characterized primarily by ESR and fibrinogen, with loadings of 0.714 and 0.642, while HGB and CRP contributed more moderately. Accordingly, this component was interpreted as the Inflammatory-Biological Component.

Thus, extension of the PCA did not simply add clinical variables to the original biological component. Instead, it revealed two partially distinct latent structures: one representing neurological and functional

severity and another representing inflammatory-biological activity. This distinction is important because it establishes the analytical basis for the subsequent CATPCA, where these domains are re-examined together with demographic, cardiovascular, metabolic, thrombolysis, and alcohol-related variables.

In Fig. 1 are presented scree plots of the biological and extended biological-clinical PCA.

Panel A: biological PCA including HGB, ESR, fibrinogen, and CRP. Panel B: extended PCA including HGB, ESR, fibrinogen, CRP, NIHSS, mRS, and GUSS.

Source Authors` Contributions

Visual inspection of the scree plots supported the dimensional solutions identified by the eigenvalue criterion: a single dominant component was evident in the biological PCA, whereas the extended biological-clinical PCA supported a two-component solution.

Taken together, the two PCA models indicate that the inflammatory markers share an identifiable biological structure, while incorporation of NIHSS, mRS, and GUSS reveals a broader organization in which biological inflammation and neurological-functional impairment emerge as related but distinguishable dimensions. These findings provide the multidimensional basis for examining whether the inflammatory profile is associated with clinical severity and functional status.

3.2. Integrated Multidimensional Profile Assessed by CATPCA

CATPCA identified a coherent two-dimensional structure integrating demographic characteristics, cardiovascular and metabolic conditions, thrombolysis, documented alcohol status, inflammatory biomarkers, and neurological/functional measures. Dimension 1 had an eigenvalue of 3.527 and Cronbach's α of 0.759, while Dimension 2 had an eigenvalue of 2.661 and α of 0.661. Overall internal consistency of the two-dimensional solution was high ($\alpha = 0.888$).

Loading patterns allowed the two dimensions to be interpreted clinically rather than retained as purely numerical axes. Dimension 1 was designated the Inflammatory-Neurological Severity Dimension, reflecting the close alignment of neurological impairment, functional status, and inflammatory activity. GUSS, NIHSS, and mRS showed the strongest loadings (0.779, 0.777, and 0.757), while fibrinogen and ESR also contributed substantially (0.655 and 0.623). CRP and HGB contributed more moderately, with loadings of 0.462 and 0.447.

This pattern indicates that inflammatory activity and clinical severity were not represented as independent phenomena within the integrated model. Rather, the strongest inflammatory markers aligned with the same latent dimension as neurological deficit and functional impairment.

Table 3 presents the complete loading pattern underlying these two clinically interpretable dimensions.

Table 3
CATPCA component loadings for the integrated clinical profile

Variable	Dimension 1: Inflammatory-Neurological Severity	Dimension 2: Age-Cardiovascular Profile
SEX	0.155	-0.446
AGE	0.384	0.617
URBAN	0.265	0.149
HTA	0.099	-0.051
Atrial fibrillation	0.017	0.523
IHD	0.097	0.218
Metabolic disease	0.150	-0.194
Mixed dyslipidemia	0.072	0.417
Obesity	-0.097	0.332
Thrombolysis	0.397	-0.204
Documented alcohol status	0.237	-0.110
HGB	0.447	-0.409
ESR	0.623	-0.583
Fibrinogen	0.655	-0.534
CRP	0.462	-0.266
GUSS	0.779	0.337
mRS	0.757	0.495
NIHSS	0.777	0.370

Source: Authors' calculations using IBM SPSS Statistics, version 26.

Dimension 2 was designated the Age-Cardiovascular Profile Dimension, being driven primarily by age and atrial fibrillation and, to a lesser extent, by mRS, mixed dyslipidemia, and obesity. Negative loadings for ESR, fibrinogen, and HGB indicate that this dimension was not simply a second inflammatory axis, but rather represented a contrast between age-related cardiovascular characteristics and the inflammatory pattern captured predominantly by Dimension 1.

Documented alcohol status displayed modest loadings on both dimensions (0.237 and – 0.110). Accordingly, alcohol status did not define either latent dimension and should not be interpreted as a

principal determinant of the overall multidimensional phenotype. Its relatively peripheral position instead supports the subsequent targeted analysis of its relationship with individual inflammatory biomarkers.

Source Authors' Contributions

Figure 2 provides a visual representation of this structure, showing the clustering of neurological and inflammatory variables along the Inflammatory-Neurological Severity Dimension, while age and selected cardiovascular characteristics extend more strongly along the Age-Cardiovascular Profile Dimension.

Within this integrated framework, neurological and functional measures remained closely aligned with the principal biological markers, whereas documented alcohol status contributed only modestly to either dimension. The CATPCA solution therefore supported the biological-clinical structure identified by conventional PCA while indicating that alcohol status was not a major determinant of the overall multidimensional profile. This finding motivated the subsequent targeted assessment of specific biological and clinical differences between ALCOHOL = 1 and ALCOHOL = 2.

3.3. Biological and Clinical Profiles According to Documented Alcohol Status

Targeted between-group analysis was undertaken to determine whether the multidimensional pattern identified previously was accompanied by measurable differences in inflammatory markers or clinical severity according to documented alcohol status. This analysis directly addressed RQ4, concerning differences in inflammatory profiles between alcohol-status categories, and provided the empirical basis for RQ5, which examined whether any observed alcohol-inflammation association persisted after adjustment for potential confounders.

Among the 71 patients, 54 were classified as ALCOHOL = 1 and 17 as ALCOHOL = 2. Complete observations were available for HGB, ESR, fibrinogen, CRP, GUSS, mRS, and NIHSS. Age distributions were comparable between the two groups (Mann-Whitney $U = 454.5$, $p = 0.949$), reducing the likelihood that the subsequent unadjusted group differences merely reflected a marked imbalance in age category.

Comparison across the biological and clinical variables revealed a selective rather than generalized between-group pattern. Higher mean ranks were observed for ALCOHOL = 2 across several inflammatory and functional measures, but statistical significance was reached only for CRP. Mean CRP rank was 45.74 in ALCOHOL = 2 compared with 32.94 in ALCOHOL = 1 ($U = 293.5$, $Z = -2.231$, $p = 0.026$). ESR showed the same directional pattern, with higher ranks in ALCOHOL = 2 (43.85 vs. 33.53), although the difference did not meet the predefined significance threshold ($p = 0.072$). Fibrinogen was likewise higher in rank in ALCOHOL = 2, but the between-group difference was not statistically significant ($p = 0.171$).

Clinical severity measures did not show statistically significant differences according to alcohol status. NIHSS yielded $p = 0.422$, while GUSS and mRS yielded $p = 0.134$ and $p = 0.084$, respectively. HGB also did not differ significantly between groups ($p = 0.526$).

Taken together, these findings indicate that documented alcohol status was not associated with a broad shift across all biological and neurological variables. Instead, the between-group signal was concentrated primarily in CRP. This is important in relation to the preceding CATPCA findings: alcohol status did not define either of the major latent dimensions, yet the targeted comparison identified a specific association with one component of systemic inflammation. The results therefore refine, rather than contradict, the multidimensional analysis.

Table 4 summarizes this selective pattern.

Table 4
Biological and clinical comparisons according to documented alcohol status

Variable	Mean rank, ALCOHOL = 1 (n = 54)	Mean rank, ALCOHOL = 2 (n = 17)	Mann-Whitney U	Z	p
HGB	35.13	38.76	412.0	-0.634	0.526
ESR	33.53	43.85	325.5	-1.800	0.072
Fibrinogen	34.12	41.97	357.5	-1.368	0.171
CRP	32.94	45.74	293.5	-2.231	0.026
GUSS	34.01	42.32	351.5	-1.500	0.134
mRS	33.70	43.29	335.0	-1.726	0.084
NIHSS	34.90	39.50	399.5	-0.803	0.422
AGE	35.92	36.26	454.5	-0.063	0.949
<p><i>Note: Values are presented as mean ranks. U denotes the Mann-Whitney U statistic and Z the standardized test statistic. p-values refer to two-sided tests, with $p < 0.05$ considered statistically significant. HGB, hemoglobin; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; GUSS, Gugging Swallowing Screen; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale. ALCOHOL = 1 and ALCOHOL = 2 represent the two documented alcohol-status categories used in the study database.</i></p>					

Source: Authors' calculations using IBM SPSS Statistics, version 26.

As shown in Table 4, CRP was the only variable for which the difference between the two alcohol-status categories reached statistical significance. Higher ranks for ESR, fibrinogen, GUSS, and mRS in ALCOHOL = 2 indicate a broadly concordant direction of variation, but these differences were insufficient to support a generalized inflammatory or clinical-severity effect. Visual inspection of CRP distributions was used to complement the rank-based comparison (Fig. 3).

Source: Authors' calculations using IBM SPSS Statistics, version 26.

Boxplots illustrate CRP distributions for ALCOHOL = 1 and ALCOHOL = 2, including median, interquartile range, and extreme values.

The distributional pattern shown in Fig. 3 was consistent with the Mann-Whitney analysis, with higher CRP values observed in the ALCOHOL = 2 group despite substantial within-group variability. Because CRP was the only biomarker showing a statistically significant between-group difference, it was selected for the subsequent multivariable analysis. This approach allowed assessment of whether the association between documented alcohol status and systemic inflammation persisted after adjustment for age, sex, obesity, and metabolic disease.

3.4. Multivariable Analysis of CRP

The between-group analysis identified CRP as the only biological marker showing a statistically significant difference between the two documented alcohol-status categories. To determine whether this association persisted after accounting for relevant demographic and metabolic characteristics, CRP was log-transformed and subsequently examined using linear regression. Mean LN_CRP was 1.0305 in ALCOHOL = 1 and 1.7514 in ALCOHOL = 2, preserving the direction of the difference observed in the non-parametric analysis.

In the unadjusted model, documented alcohol status was significantly associated with LN_CRP ($B = 0.721$, $SE = 0.324$, standardized $\beta = 0.259$, $t = 2.226$, $p = 0.029$; 95% CI, 0.075–1.367). Alcohol status alone accounted for 6.7% of the observed variance in LN_CRP ($R^2 = 0.067$; adjusted $R^2 = 0.053$), with the model reaching statistical significance ($F = 4.955$, $p = 0.029$).

Adjustment for age, sex, obesity, and metabolic disease did not materially attenuate the alcohol-status coefficient. Its magnitude remained similar to that observed in the unadjusted analysis ($B = 0.732$, $SE = 0.331$, standardized $\beta = 0.263$), and the coefficient remained statistically significant ($t = 2.210$, $p = 0.031$; 95% CI, 0.071–1.394). None of the four covariates showed an independent statistically significant association with LN_CRP. Multicollinearity was not evident, with VIF values ranging from 1.007 to 1.186.

Table 5 shows that the stability of the ALCOHOL coefficient across the two models is more notable than any increase in overall explanatory performance. Addition of the covariates increased R^2 only from 0.067 to 0.086, while adjusted R^2 decreased from 0.053 to 0.016. Moreover, although the individual coefficient for documented alcohol status remained statistically significant, the adjusted model as a whole was not statistically significant ($F = 1.227$, $p = 0.307$). The association should therefore be interpreted as a specific adjusted signal within a model of limited overall explanatory capacity, rather than evidence that the included predictors collectively provide a strong explanation of CRP variability.

Table 5
Linear regression models for log-transformed CRP

Predictor	B	SE	Standardized β	t	p	95% CI for B
Unadjusted model						
ALCOHOL	0.721	0.324	0.259	2.226	0.029	0.075 to 1.367
Adjusted model						
ALCOHOL	0.732	0.331	0.263	2.210	0.031	0.071 to 1.394
Age	-0.051	0.150	-0.044	-0.339	0.736	-0.352 to 0.249
Sex	0.223	0.311	0.093	0.720	0.474	-0.397 to 0.844
Obesity	0.009	0.288	0.004	0.033	0.974	-0.566 to 0.585
Metabolic disease	0.200	0.317	0.077	0.631	0.530	-0.433 to 0.834
<p><i>Note: B, unstandardized regression coefficient; SE, standard error; β, standardized regression coefficient; CI, confidence interval. Dependent variable: natural logarithm of C-reactive protein (LN_CRP). Statistical significance was defined as $p < 0.05$. Unadjusted model: $R^2 = 0.067$, adjusted $R^2 = 0.053$, $F = 4.955$, $p = 0.029$. Adjusted model: $R^2 = 0.086$, adjusted $R^2 = 0.016$, $F = 1.227$, $p = 0.307$. ALCOHOL = 1 and ALCOHOL = 2 represent the two documented alcohol-status categories used in the study database.</i></p>						

Source: Authors' calculations using IBM SPSS Statistics, version 26.

Model diagnostics were examined to assess whether the regression results were compatible with the assumptions underlying the linear model. Standardized residuals showed no marked departure from the expected distribution, while the normal probability plot indicated an overall acceptable correspondence between observed residuals and the theoretical normal distribution (Fig. 4). These findings supported use of the fitted model for the adjusted analysis, although they do not alter its limited explanatory capacity.

Panel A: distribution of standardized residuals. Panel B: normal P-P plot of standardized residuals.

Source: Authors' calculations using IBM SPSS Statistics, version 26.

Taken together, the regression analyses confirmed the pattern identified in the preceding between-group comparison. The association between documented alcohol status and CRP persisted after adjustment for age, sex, obesity, and metabolic disease, with little change in coefficient magnitude. However, the small proportion of explained variance and the non-significant overall adjusted model indicate that CRP

variability cannot be attributed predominantly to the variables included in this model. The finding therefore supports a specific association between documented alcohol status and the inflammatory profile, while its magnitude and explanatory relevance require cautious interpretation.

4. Discussion

Findings of the present study delineate acute ischemic stroke (AIS) as a multidimensional clinical condition in which systemic inflammatory activity, neurological and functional impairment, cardiovascular characteristics, significance for further carotid artery metabolism, and documented alcohol status contribute differently to patient heterogeneity. Biological PCA identified a common inflammatory-biological structure, whereas incorporation of neurological and functional measures revealed a separation between biological activity and clinical severity. CATPCA subsequently placed these domains within a broader patient profile and showed that documented alcohol status was not a major determinant of overall multidimensional variation. Nevertheless, targeted analyses identified a specific association between alcohol status and CRP, which persisted after adjustment for selected demographic and metabolic covariates [6,19,20].

This combination of findings is central to the interpretation of the study. Inflammation was clearly embedded in the AIS phenotype, but no single inflammatory marker adequately represented its complexity. Neurological-functional severity constituted a closely related yet distinguishable domain, while alcohol status appeared to be associated with a specific inflammatory signal rather than with a generalized inflammatory or neurological phenotype. Such a pattern is consistent with the multifactorial nature of AIS, in which inflammatory, vascular, metabolic, and clinical processes interact without necessarily varying in parallel [1,2,9,10].

4.1. Systemic Inflammatory Profile in Acute Ischemic Stroke

The biological PCA addressed the inflammatory profile underlying the investigated AIS cohort and identified a single component encompassing HGB, ESR, fibrinogen, and CRP. More than half of the total biological variance was represented by this component, indicating that the four routinely available markers shared a meaningful underlying structure rather than behaving as entirely independent measurements.

ESR and fibrinogen were the strongest contributors to this component, while CRP and HGB showed more moderate contributions. This hierarchy is relevant because the inflammatory response to cerebral ischemia involves multiple interconnected pathways. Ischemic injury induces endothelial activation, recruitment of inflammatory cells, disruption of the blood-brain barrier, and both local and systemic inflammatory responses [9,10]. Consequently, circulating biomarkers may reflect different aspects of the same biological process rather than equivalent measures of a single inflammatory mechanism [1,6,11,17,23].

Fibrinogen occupies a particularly important position in this context because it connects inflammatory activation with coagulation and thrombotic processes. ESR provides a less specific measure of systemic inflammatory activity, while CRP represents an acute-phase response that has been associated with vascular inflammation and disruption of blood-brain barrier integrity [11]. Their convergence within the same component therefore supports the presence of an integrated inflammatory-biological profile in AIS [5].

An important feature of the present findings is that CRP was not the dominant marker within this global biological structure. ESR and fibrinogen contributed more strongly to the latent component, suggesting that characterization of inflammation in AIS should not be reduced to CRP alone. This observation becomes particularly relevant when considered alongside the alcohol-specific analyses, in which CRP subsequently emerged as the only marker showing a statistically significant between-group difference. Thus, the marker that best differentiates a particular clinical exposure does not necessarily have to be the marker that contributes most strongly to overall inflammatory variability.

Regarding the first research question, the cohort can therefore be characterized by a coherent but heterogeneous systemic inflammatory-biological profile, dominated by ESR and fibrinogen and complemented by CRP and HGB. The findings support the collective interpretation of routinely available biomarkers while preserving their individual biological significance.

4.2. Inflammatory Activity and Neurological-Functional Severity

Incorporation of NIHSS, mRS, and GUSS substantially changed the dimensional organization of the data. The extended PCA supported two components rather than the single component identified in the biological model. Neurological deficit, disability, and swallowing impairment clustered strongly together, whereas the inflammatory markers, particularly ESR and fibrinogen, contributed more prominently to a second component [19,20,21].

Such a configuration provides an important answer to the second and third research questions. NIHSS, mRS, and GUSS represent clinically different aspects of AIS, yet their strong convergence indicates that they captured a common neurological-functional severity construct within the investigated population. This is consistent with the clinical course of stroke, in which neurological deficit, functional dependence, and swallowing impairment frequently coexist as manifestations of the extent and consequences of cerebral injury [4].

Systemic inflammatory activity, however, was not simply another representation of neurological severity. Separation of the inflammatory-biological and neurological-functional components indicates that the two domains were related within the overall AIS phenotype but retained substantial independent variation. A patient may therefore present marked neurological or functional impairment without an equally pronounced systemic inflammatory response, while another may display substantial inflammatory activity that is not proportional to neurological severity.

A clinically illustrative case within the analyzed cohort further emphasizes the partial dissociation between neurological expression and systemic inflammatory activity. One of the 71 patients, an 84-year-old man, presented with confusion, delirium, and aphasia in the context of an acute ischemic stroke. During the acute neurobehavioral episode, the patient ingested several small metallic springs from his home workshop, an event that was not directly witnessed by his relatives. The uncertain time of stroke onset precluded intravenous thrombolysis. Neurological deficit was moderate at presentation (NIHSS = 6) and improved during hospitalization (NIHSS = 3 at discharge), while the delirium resolved approximately 12 hours after admission. Despite the marked neurological and behavioral manifestations, inflammatory markers were not elevated; ESR and the neutrophil-to-lymphocyte ratio remained within normal ranges (Fig. 5) [19–22, 24–27].

Plain abdominal radiography showing multiple small metallic springs ingested during the acute confusional episode. The foreign bodies were subsequently eliminated without surgical intervention.

As this patient belonged to the analyzed cohort, the case provides a clinically tangible illustration of the heterogeneity captured by the multidimensional analyses. It does not constitute independent evidence beyond the cohort-level findings, but illustrates how substantial neurological and neurobehavioral manifestations may coexist with a limited systemic inflammatory response. This observation is consistent with the separation identified by the extended PCA between the Neurological-Functional Severity Component and the Inflammatory-Biological Component, reinforcing the interpretation that systemic inflammatory activity and clinical stroke expression represent related but non-equivalent dimensions of the acute ischemic stroke phenotype.

Conventional PCA therefore provides more than dimensional reduction. It suggests that the clinical expression of AIS is organized around at least two distinguishable domains: an Inflammatory-Biological Component and a Neurological-Functional Severity Component. Their partial separation offers a clinically interpretable explanation for why individual biomarkers cannot be expected to reproduce the entire spectrum of neurological severity.

4.3. Integrated Multidimensional Clinical Profile

CATPCA expanded this interpretation by incorporating demographic characteristics, cardiovascular and metabolic conditions, thrombolysis, documented alcohol status, biological markers, and neurological-functional measures into the same analytical framework. Two broader dimensions emerged: an Inflammatory-Neurological Severity Dimension and an Age-Cardiovascular Profile Dimension.

The apparent convergence of biological and neurological measures within the first CATPCA dimension does not contradict their partial separation in conventional PCA. Rather, the two approaches address the structure of the data at different levels. PCA characterized relationships among the principal continuous biological and clinical measures, whereas CATPCA evaluated these domains within a heterogeneous set of categorical, ordinal, and continuous patient characteristics. Together, the analyses indicate that

inflammatory and neurological-functional domains retain internal differentiation while becoming aligned when considered as components of the broader AIS phenotype.

This complementarity represents an important methodological and substantive finding. It suggests that the multidimensional organization of AIS depends partly on the level at which the clinical phenotype is examined. At a focused biological-clinical level, inflammatory activity and neurological severity can be distinguished. Within the integrated patient profile, however, they participate in a common dominant dimension. The results therefore provide a positive answer to the third research question concerning whether the investigated characteristics could be reduced to clinically interpretable latent dimensions.

Age and atrial fibrillation were particularly relevant to the second CATPCA dimension, together with more moderate contributions from mRS, mixed dyslipidemia, and obesity. This pattern supports the existence of a separate demographic-cardiovascular context contributing to heterogeneity among patients with AIS. Cardiovascular and metabolic conditions are recognized components of the complex risk environment in which cerebral ischemia occurs [4,15], and their integration into a distinct multidimensional profile is therefore clinically plausible [6–8,23,28].

Loadings observed for individual cardiovascular variables should nevertheless not be interpreted as measures of etiological importance. CATPCA describes how variables contribute to variation within the studied cohort rather than their causal contribution to stroke development. A highly prevalent risk factor may therefore contribute relatively little to discrimination between patients despite its established clinical relevance.

Taken together, these findings address the sixth research question by demonstrating that age, cardiovascular, metabolic, and therapeutic characteristics contribute to the multidimensional organization of AIS but do not replace the principal inflammatory-neurological structure. The resulting phenotype is therefore best understood as the coexistence of several interrelated clinical domains rather than as a single severity continuum.

4.4. Documented Alcohol Status and the Inflammatory Profile

Documented alcohol status occupied only a peripheral position within the CATPCA solution. Its relatively modest contribution to both dimensions indicates that alcohol status did not define the overall inflammatory-neurological or age-cardiovascular phenotype of the cohort. This is an important negative finding because it limits interpretations in which documented alcohol status would be considered a dominant organizing characteristic of the clinical presentation [16].

Targeted between-group analyses, however, revealed a more specific association. CRP was the only biological or neurological-functional variable showing a statistically significant difference between ALCOHOL = 1 and ALCOHOL = 2. ESR showed a directionally similar difference but did not reach

statistical significance, while fibrinogen and HGB were not significantly different. Likewise, NIHSS, mRS, and GUSS did not differ significantly according to alcohol status.

The fourth research question is therefore answered by a selective rather than generalized pattern. Documented alcohol status was associated with CRP, but not with a consistent shift across the entire inflammatory profile or with significantly greater neurological-functional severity. This distinction is important because a statistically significant CRP difference should not be extrapolated into evidence of globally enhanced inflammation among patients in ALCOHOL = 2.

The absence of significant differences in NIHSS, mRS, and GUSS further indicates that the CRP association was not accompanied by a demonstrably different neurological-functional presentation. Within the limitations of the available sample, patients in the two alcohol-status categories therefore differed more clearly at the level of one inflammatory marker than at the level of measured neurological severity, disability, or swallowing impairment.

This finding also establishes a meaningful connection between CATPCA and the targeted group analysis. CATPCA indicated that alcohol status was not a major determinant of the global phenotype, whereas the Mann-Whitney analysis identified a specific CRP-related difference. These results are complementary. An exposure may have little influence on overall multidimensional variation while remaining associated with a particular biological characteristic.

Interpretation of the alcohol variable requires particular caution. The retrospective database recorded documented alcohol status, rather than a standardized quantitative measure of alcohol exposure. Information regarding amount, frequency, duration, drinking pattern, and cumulative exposure was not available with sufficient consistency. Accordingly, ALCOHOL = 1 and ALCOHOL = 2 should remain the analytical categories used in reporting, rather than being translated into stronger clinical labels that the database cannot support.

The distinction is particularly relevant in neurological practice because acute confusion, delirium, or other behavioral manifestations cannot automatically be attributed to alcohol exposure. Such manifestations may result from the cerebral ischemic event itself and may coexist with nutritional, metabolic, social, or other vulnerabilities. The clinical case described above illustrates this complexity and supports analytical separation between documented alcohol status, systemic inflammatory activity, and acute neurological expression rather than their incorporation into a single presumed pathway [19–22,24–27,29–32].

4.5. Alcohol Status and CRP After Multivariable Adjustment

The significant between-group difference in CRP provided the rationale for examining whether this association persisted after adjustment for selected potential confounders. Analysis of log-transformed

CRP demonstrated a positive alcohol-status coefficient in the unadjusted model, which remained statistically significant after adjustment for age, sex, obesity, and metabolic disease [23,28].

Stability of the coefficient across the two models is noteworthy. Adjustment produced little change in either its magnitude or direction, suggesting that the observed association was not substantially attenuated by the covariates included in the analysis. This finding provides qualified support for the fifth research question: the association between documented alcohol status and CRP persisted after adjustment for the selected demographic and metabolic characteristics.

Interpretation must nevertheless account for the overall performance of the multivariable model. Although the alcohol coefficient remained statistically significant, the adjusted model as a whole did not reach statistical significance and explained only a limited proportion of CRP variability. The result should therefore not be presented as evidence that the included variables provide a satisfactory explanatory model of systemic inflammation.

This distinction is particularly important for avoiding causal overinterpretation. Persistence of an individual coefficient after covariate adjustment indicates a statistical association conditional on the variables included in the model; it does not establish an independent causal effect of alcohol exposure on CRP. Residual confounding remains possible, particularly given the retrospective design and the limited characterization of alcohol exposure.

Nevertheless, convergence between the non-parametric comparison and regression analysis strengthens the internal consistency of the CRP finding. CRP emerged as the only significantly different marker in the group comparison, and the corresponding association persisted after transformation and adjustment. The signal was therefore observed through two analytical approaches rather than arising from a single statistical procedure.

An additional insight follows from comparison with the PCA results. CRP was not the strongest determinant of the general inflammatory-biological component, where ESR and fibrinogen were more prominent. Yet CRP became the marker most clearly related to documented alcohol status. This suggests that importance within a latent biological structure and sensitivity to a specific exposure are not equivalent properties. A marker may contribute moderately to overall biological variability while still distinguishing a clinically relevant subgroup.

4.6. Integration of the Research Questions and Principal Contribution

Considered together, the six research questions describe a coherent progression from the global biological organization of AIS to a specific alcohol-related inflammatory association.

The inflammatory profile was structured rather than fragmented, with ESR and fibrinogen providing the strongest representation of the shared biological component. Addition of NIHSS, mRS, and GUSS demonstrated that neurological-functional severity constituted a coherent clinical domain that was

distinguishable from systemic inflammatory activity. CATPCA subsequently showed how these domains were integrated within the wider demographic, cardiovascular, metabolic, therapeutic, and behavioral profile of the patients.

Within this broader architecture, documented alcohol status did not define a major multidimensional phenotype. Its association was considerably more specific: CRP differed between the two alcohol-status categories and the corresponding coefficient persisted after adjustment for age, sex, obesity, and metabolic disease, while neurological-functional measures did not differ significantly.

This pattern constitutes the principal contribution of the study. Existing evidence has established the importance of inflammation in cerebral ischemia [1,2,9–11], while cardiovascular, metabolic, and lifestyle factors form part of the broader AIS risk environment [4,15]. The present analysis adds a different perspective by examining these elements at several interconnected levels rather than treating them as isolated predictors [5,6,8,16–18,33].

The complementary use of PCA and CATPCA was particularly informative in this respect. Conventional PCA identified the internal organization of the principal continuous biological and neurological-functional measures, while CATPCA positioned them within the heterogeneous clinical profile. Targeted group comparison then isolated the variable associated with documented alcohol status, and multivariable regression assessed whether that specific association persisted after adjustment.

The analytical sequence therefore moved from latent structure to subgroup differentiation and subsequently to adjusted association. This is relevant because it prevents the CRP finding from being interpreted in isolation. CRP was not selected arbitrarily as the principal outcome; it emerged from the comparison between alcohol-status categories after the multidimensional analyses had already established the broader organization of the cohort.

A clinically relevant implication is that inflammatory biomarkers should not necessarily be considered interchangeable. ESR and fibrinogen were particularly informative for defining the latent inflammatory-biological structure, whereas CRP provided the clearest differentiation according to documented alcohol status. Different biomarkers may therefore convey different information depending on whether the clinical question concerns the global inflammatory phenotype, neurological-functional integration, or association with a particular patient characteristic.

The study consequently does not support a simple sequence in which documented alcohol status produces generalized inflammation that subsequently determines neurological severity. Instead, the findings favor a more differentiated interpretation: systemic inflammation forms an important component of AIS, neurological-functional severity represents a closely related but partially distinct domain, and documented alcohol status is associated with a specific CRP signal without defining the overall multidimensional phenotype.

4.7. Clinical and Research Implications

Several implications can be derived from this pattern. Routine inflammatory markers may provide complementary information in AIS, but their clinical interpretation should consider the biological question being addressed. Fibrinogen and ESR appeared particularly informative for the general inflammatory structure, while CRP may be more sensitive to specific differences associated with documented alcohol status [1,5,10,11]. The broader clinical context is also informed by evidence on reperfusion and stroke care, vascular imaging, systemic comorbidity, environmental and One Health determinants [34–43].

Neurological and functional scales similarly provide information that cannot be inferred directly from systemic inflammatory markers. The strong coherence among NIHSS, mRS, and GUSS supports their representation of a common clinical severity domain, whereas their partial separation from the inflammatory component cautions against assuming that inflammatory biomarker elevation is a direct proxy for neurological impairment.

Documented alcohol status may therefore be relevant to inflammatory characterization without necessarily identifying a distinct neurological severity phenotype. Confirmation of this finding would require prospective assessment of alcohol exposure using standardized measures capable of distinguishing frequency, amount, duration, and drinking pattern. Such characterization would also allow examination of potential dose-response relationships that cannot be evaluated from the present binary retrospective variable.

Future studies could further determine whether CRP represents a transient acute-phase difference, a marker of pre-existing systemic inflammatory conditions, an indirect correlate of alcohol-associated nutritional or metabolic factors, or a component of a more specific biological response to cerebral ischemia. Repeated biomarker measurements and prospective follow-up would be particularly valuable for distinguishing these possibilities [11,16].

4.8. Limitations

Several limitations affect the interpretation of the findings. The retrospective, observational, single-center design restricts control over data acquisition and limits generalizability beyond the population from which the cohort was derived. The sample size was modest, comprising 71 patients, and the alcohol-status groups were unequal, with 54 observations in ALCOHOL = 1 and 17 in ALCOHOL = 2. Statistical estimates, particularly those obtained from multivariable analyses, should consequently be interpreted with appropriate caution.

Characterization of alcohol exposure represents a major limitation. Alcohol status was obtained from routine clinical documentation and did not provide standardized information regarding quantity, frequency, duration, type of alcohol consumed, drinking pattern, or cumulative exposure. Chronic alcoholism was separately recorded but occurred too infrequently to support meaningful multivariable analysis. The findings therefore relate specifically to documented alcohol status and cannot be extrapolated to alcohol-use disorder, alcohol dependence, or defined levels of alcohol consumption.

Inflammatory characterization was based on routinely available markers. CRP, ESR, fibrinogen, and HGB provide clinically accessible biological information but do not capture the full complexity of inflammatory responses following cerebral ischemia, which involve cytokine signaling, endothelial activation, immune-cell recruitment, and neuroinflammatory mechanisms [1,9–11]. Variation in the timing of laboratory sampling relative to stroke onset may also have influenced measured inflammatory activity [6].

Residual confounding remains possible in the CRP analysis. Age, sex, obesity, and metabolic disease were incorporated into the adjusted model, but other determinants of CRP were not comprehensively represented. The limited R^2 and non-significant global adjusted model indicate that most variability in LN_CRP remained unexplained. The persistent alcohol coefficient should consequently be regarded as an adjusted association within the specified model rather than evidence of a causal relationship.

PCA and CATPCA were exploratory and sample-dependent. Although both yielded clinically interpretable structures, the identified components and dimensions require replication in larger independent populations before they can be considered stable latent phenotypes. The moderate KMO values observed in conventional PCA similarly favor cautious interpretation rather than strong claims of definitive dimensional structure.

Clinical scales and diagnoses were derived retrospectively from available medical documentation. Acute neurological manifestations may also be influenced by factors not completely represented in the database, including nutritional condition, metabolic abnormalities, pre-existing cognitive status, social vulnerability, and other acute clinical complications. The delirium case, although originating from the analyzed cohort, represents an individual clinical trajectory and should not be generalized to the remaining patients. Its role in the present study is illustrative, providing a patient-level example of the heterogeneity identified statistically between systemic inflammatory activity and neurological-functional expression [23,44,45].

Causal and temporal relationships cannot be established from the present design. Whether alcohol-related characteristics precede or modify systemic inflammatory activation, whether inflammation contributes to neurological evolution, or whether both reflect other underlying patient characteristics cannot be determined from these data. Prospective studies with standardized exposure assessment, predefined biomarker sampling, longitudinal neurological evaluation, and broader inflammatory profiling are required to address these mechanisms.

4.9. Overall Interpretation

An integrated interpretation of the findings indicates that AIS in this cohort was characterized by a recognizable systemic inflammatory-biological structure and a coherent neurological-functional severity domain. These domains were partially distinguishable in conventional PCA but became aligned within the broader multidimensional phenotype identified by CATPCA. Age and cardiovascular characteristics contributed an additional dimension of patient heterogeneity.

Documented alcohol status did not emerge as a major determinant of this overall multidimensional organization. Instead, its principal signal was selective and centered on CRP. The between-group CRP difference was supported by the subsequent regression analysis, in which the alcohol-status coefficient remained statistically significant after adjustment for age, sex, obesity, and metabolic disease. This association occurred without statistically significant differences in NIHSS, mRS, or GUSS and without evidence that alcohol status defined the broader inflammatory or neurological phenotype.

Taken together, the results suggest that documented alcohol status in AIS may be associated with a specific component of systemic inflammatory activity rather than with generalized inflammatory activation or greater neurological-functional severity. This distinction provides the principal interpretative contribution of the study and offers a basis for prospective investigation using more precise characterization of alcohol exposure and longitudinal inflammatory assessment.

The findings ultimately support a multidimensional view of AIS in which inflammatory biology, neurological-functional expression, cardiovascular context, and behavioral characteristics interact but should not be considered interchangeable. Recognition of these distinct yet interconnected domains may provide a more informative framework for interpreting the heterogeneity encountered in routine clinical populations.

5. Conclusions

Acute ischemic stroke in this cohort was characterized by a multidimensional profile in which systemic inflammatory activity and neurological-functional impairment were related but distinguishable components of the clinical phenotype. ESR and fibrinogen provided the strongest representation of the biological-inflammatory structure, whereas NIHSS, mRS, and GUSS defined a coherent neurological-functional dimension. Extension of the analysis through CATPCA confirmed this organization within a broader demographic, cardiovascular, metabolic, biological, and clinical framework.

Documented alcohol status did not emerge as a dominant determinant of the overall multidimensional phenotype. Its association was more selective, with CRP being the only investigated biological or clinical variable that differed significantly between ALCOHOL = 1 and ALCOHOL = 2. This relationship remained statistically significant after adjustment for age, sex, obesity, and metabolic disease, although the limited explanatory capacity and non-significant overall adjusted model require cautious interpretation.

These findings suggest that the relationship between documented alcohol status and acute ischemic stroke should not be interpreted as a generalized shift in inflammatory or neurological severity. Rather, the observed pattern points toward a more specific association with CRP within an otherwise heterogeneous biological and clinical profile. The absence of corresponding significant differences in ESR, fibrinogen, NIHSS, mRS, and GUSS further supports this selective rather than global interpretation.

Integration of conventional PCA, CATPCA, group comparisons, and multivariable modelling represents a principal contribution of the study, allowing the inflammatory profile to be examined both as part of the

broader stroke phenotype and in relation to documented alcohol status. Within the limitations of a retrospective, single-center study and a relatively small cohort, the results provide an exploratory framework for identifying clinically relevant inflammatory patterns that may not be apparent when individual biomarkers are considered in isolation.

Larger prospective studies incorporating quantitative characterization of alcohol exposure, temporal assessment of inflammatory biomarkers, nutritional status, stroke characteristics, and longitudinal functional outcomes are needed to determine whether the observed CRP association is reproducible and clinically meaningful. Such studies may clarify whether alcohol-related factors contribute to specific inflammatory pathways in acute ischemic stroke rather than to a uniform increase in systemic inflammation or neurological severity.

Declarations

Funding Declaration

There was no funding for this research project.

Author Contribution

N.a.Ț, EME and CGȘ wrote the main manuscript text, FȚ, D.I, L.I prepared figures 1-4, M.L.Z, M.D.C, D.A.C prepared table 1-5, D:E.M. prepared figure 5, C.M.V and G.G made vizualisation

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Figures

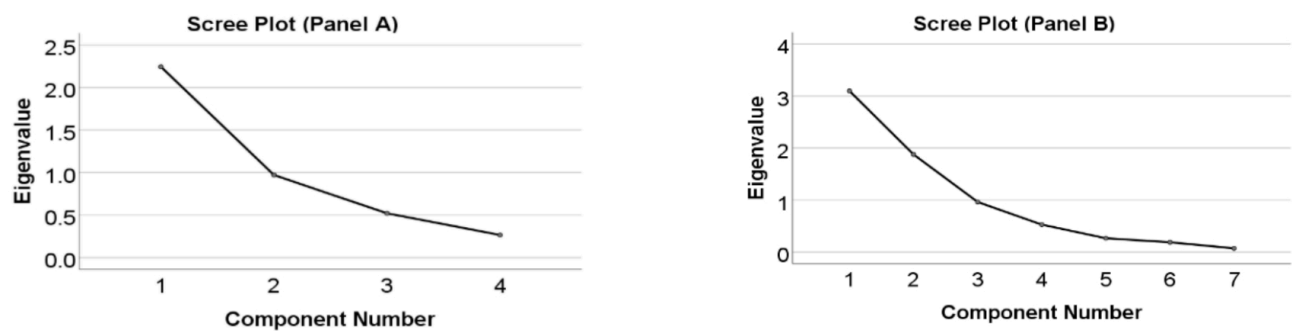


Figure 1

Scree plots of the biological and extended biological-clinical PCA.

Panel A: biological PCA including HGB, ESR, fibrinogen, and CRP. Panel B: extended PCA including HGB, ESR, fibrinogen, CRP, NIHSS, mRS, and GUSS.

Source Authors` Contributions

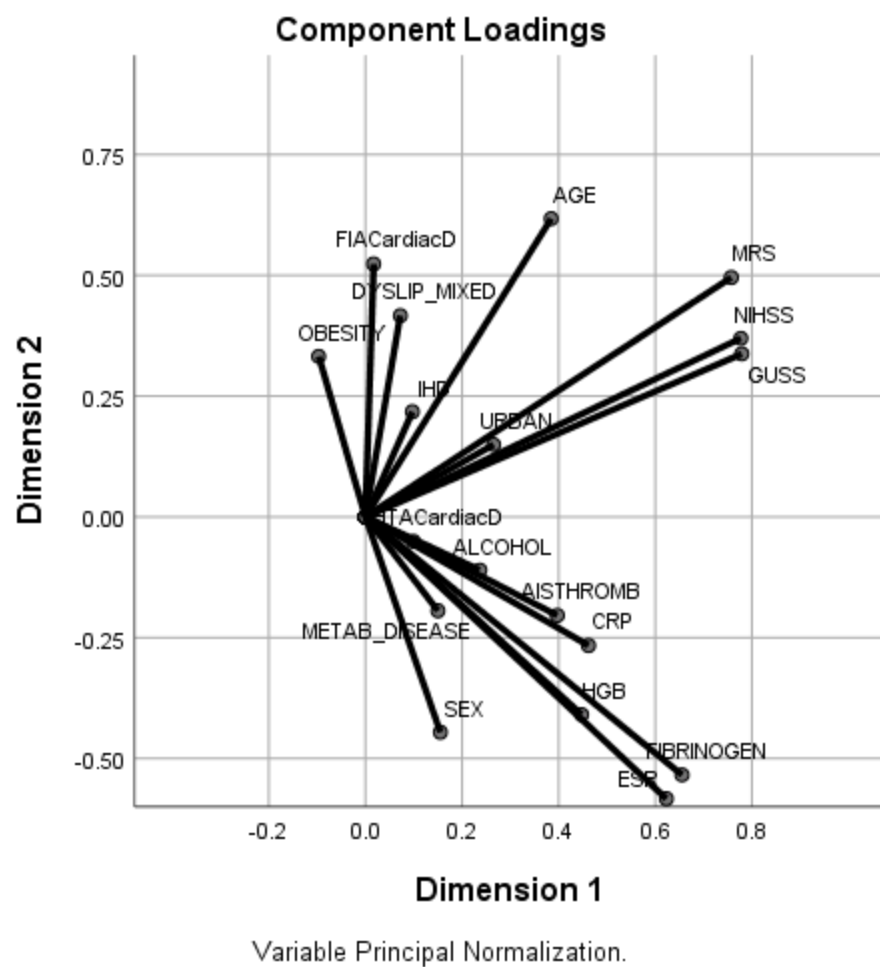


Figure 2

CATPCA loading map of the Inflammatory-Neurological Severity and Age-Cardiovascular Profile dimensions.

Source Authors` Contributions

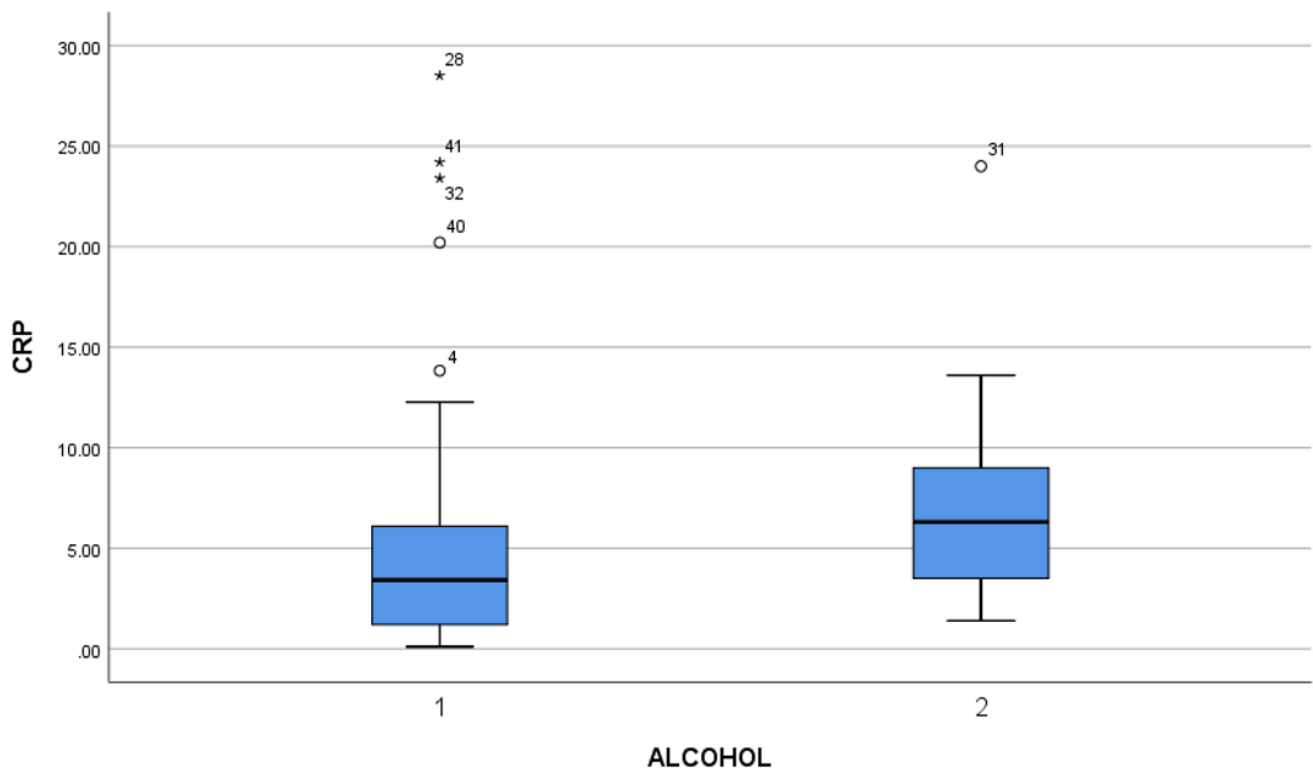


Figure 3

Distribution of C-reactive protein according to documented alcohol status.

Source: Authors' calculations using IBM SPSS Statistics, version 26.

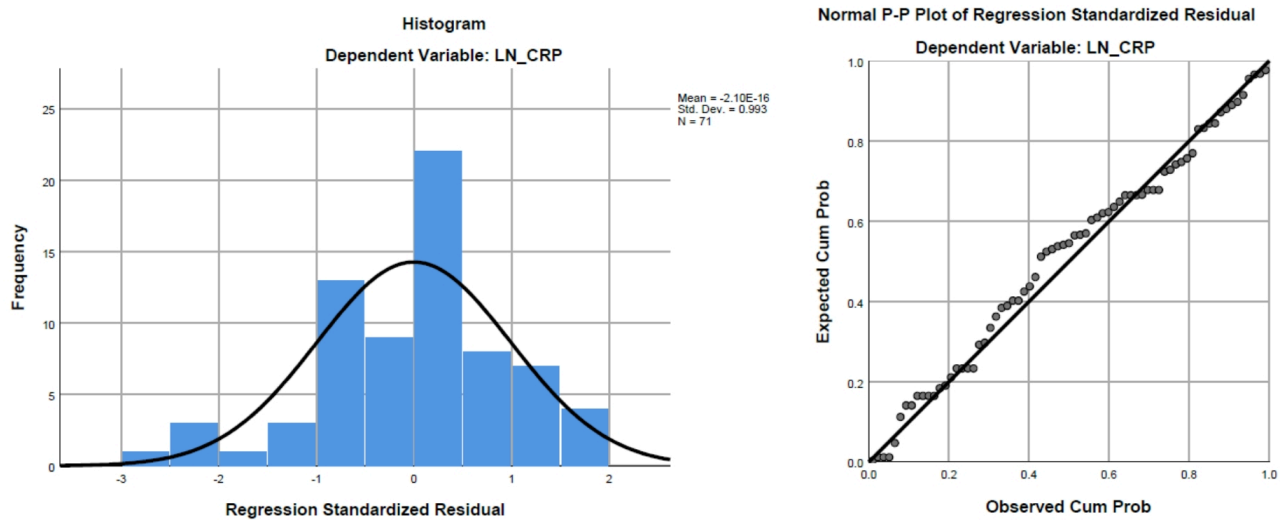


Figure 4

Diagnostic assessment of the adjusted linear regression model for LN_CRP.

Panel A: distribution of standardized residuals. Panel B: normal P-P plot of standardized residuals.

Source: Authors' calculations using IBM SPSS Statistics, version 26.

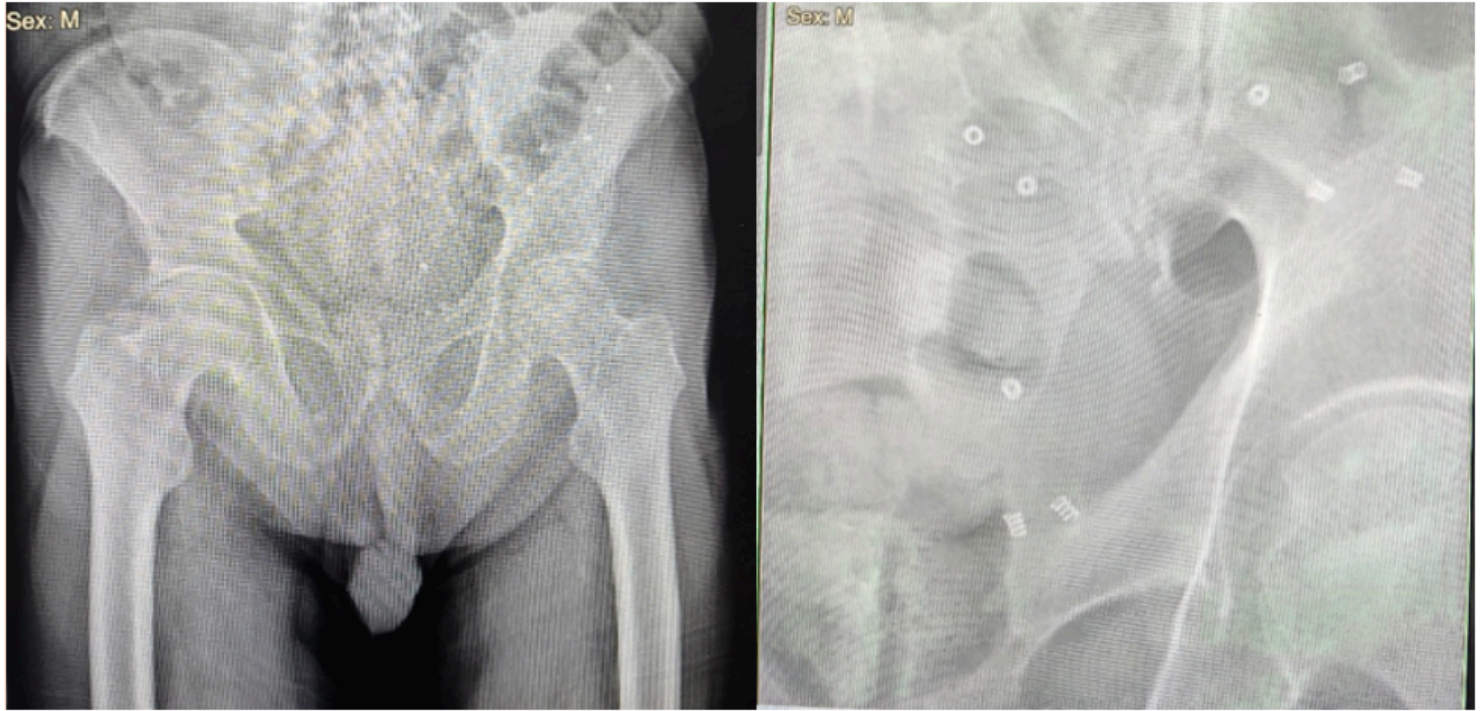


Figure 5

Abdominal radiographic findings in a patient with acute ischemic stroke and transient delirium included in the study cohort.

Plain abdominal radiography showing multiple small metallic springs ingested during the acute confusional episode. The foreign bodies were subsequently eliminated without surgical intervention.