Original Paper

Predictive Value of Pulmonary Involvement in Stroke Patients Co-Infected with COVID-19

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ABSTRACT: In response to the intricate clinical challenges posed by the intersection of COVID-19 and acute ischemic stroke, the Neuropsychiatry Hospital of Craiova, Romania, initiated a comprehensive study. This research aims to unravel the impacts of pulmonary complications on ischemic stroke outcomes, comparing patients with concurrent SARS-CoV-2 infection to those without. The study integrates pulmonary assessments, acknowledging the significant role respiratory involvement plays in the progression and prognosis of stroke patients during the pandemic. By systematically examining individuals with both acute ischemic stroke and COVID-19, the study seeks to shed light on the complex interplay between cerebral and pulmonary health. The findings are expected to enhance patient care by informing clinical decisions and leading to more effective management approaches for stroke patients in the COVID-19 era.

KEYWORDS: *Stroke, COVID, inflammation, pneumonia, Sars-CoV-2, coagulation.*

Introduction

Stroke, recognized as a significant global health concern, stands as one of the leading causes of both morbidity and mortality, imposing a substantial burden on healthcare systems and societies worldwide [1,2].

The intricate nature of this cerebrovascular event presents clinicians and researchers with a complex and multifaceted clinical challenge.

Acute ischemic stroke, in particular, demands meticulous examination and management due to its potential to inflict profound neurological deficits and lead to long-term disability in survivors [3,4,5].

The repercussions of stroke reverberate far beyond the initial onset, affecting not only the individuals afflicted but also their families, caregivers, and healthcare providers who strive to navigate the intricate path of post-stroke recovery [6,7].

However, the landscape of stroke care and management has recently witnessed the emergence of a formidable, unanticipated force-the COVID-19 pandemic [8].

The global spread of the novel coronavirus, SARS-CoV-2, has introduced an additional layer of complexity to the field of stroke medicine and rehabilitation [9,10].

The convergence of stroke and COVID-19, two distinct clinical entities, has led to a synergistic interplay that demands close scrutiny [11,12,13].

The intertwining of these two medical conditions, each possessing its unique pathophysiological characteristics, has the potential to yield unforeseen consequences, both in terms of patient outcomes and healthcare delivery [14].

In individuals afflicted by COVID-19, the virus primarily targets the respiratory system, leading to a range of clinical manifestations, from mild symptoms such as cough and shortness of breath to severe acute respiratory distress syndrome (ARDS) [15,16].

The hallmark of severe COVID-19 cases is the cytokine storm and hyperinflammatory response that may result in extensive lung damage and ultimately require mechanical ventilation [17,18,19].

This aggressive attack on the respiratory system has significantly contributed to the global morbidity and mortality associated with COVID-19 [20].

Stroke, by itself, has the potential to impact respiratory function, especially in cases where neurological deficits affect the muscles involved in breathing, and concurring infections [21,22].

However, when combined with COVID-19, the situation becomes more convoluted.

The pivotal question arises: how does the interaction between acute ischemic stroke and

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SARS-CoV-2 infection influence patient prognosis and clinical management?

Emerging evidence underscores the importance of this question, hinting at the profound implications of this dynamic relationship.

Stroke patients who are afflicted by SARS-CoV-2 may face not only the challenges posed by their neurological insult but also the added complexity of viral infection and its repercussions on various organ systems.

Materials and Methods

Ethical approval

The present study obtained authorization with registration number 202/19.10.2022 from the University of Medicine and Pharmacy of Craiova-Academic and Scientific Ethics and Deontology Committee.

This approval was granted in adherence to the Declaration of Helsinki guidelines.

All participants willingly provided the signature as an expression of their consent and willingness to take part in the ongoing research.

Research framework

This research was a prospective, single-center, cross-sectional investigation conducted at the Neuropsychiatry Hospital of Craiova from October 2022 to March 2023.

Patients, or individuals acting on their behalf, were thoroughly briefed on the study, and written consent was obtained from eligible participants.

Cohort

Patients admitted to the hospital with acute ischemic stroke diagnoses were screened to determine their eligibility for inclusion in the study.

Inclusion criteria encompassed: (1) individuals aged 18 and above, irrespective of gender; (2) those diagnosed with ischemic stroke; (3) individuals manifesting symptoms within 24 hours of onset; (4) individual's ineligible for thrombolytic therapy or mechanical thrombectomy; (5) availability of imaging data (e.g., CT scans or X-rays) to assess pulmonary involvementand; (6) individuals concurrently diagnosed with SARS-CoV-2 infection.

Conversely, exclusion criteria considered: (1) hemorrhagic stroke; (2) individuals displaying other CNS-affecting conditions (e.g., demyelinating disorders, brain tumors, prior craniotomy, and severe brain injury); (3) those with pharmacological, psychological or other factors potentially interfering with data gathering or analysis; (4) patients devoid of pulmonary involvement.

Acute ischemic stroke diagnosis relied on clinical and neurological assessments and cerebral imaging techniques (computer tomography-CT).

Additionally, pulmonary involvement was evaluated using either CT scans or X-rays.

92 patients with acute ischemic stroke in the aforementioned period participated in the study.

They were categorized into two cohorts: Control (encompassing ischemic stroke patients with pulmonary involvement-N=50) and COVID (comprising ischemic stroke patients with concurrent SARS-CoV-2-N=42).

Demographic data were collected, and a specialist with appropriate training assessed the location of the lesion, Medical Research Council (MRC) scores, modified Rankin Scale (mRS), and National Institutes of Health Stroke Scale (NIHSS) scores.

Prognostic scales

The modified Rankin Scale (mRS) adapted in the 1980s [23] is highly versatile, encompassing a wide range of functional outcomes from symptom-free recovery to mortality [24].

Its categories are user-friendly and intuitive, making it easily understandable for both healthcare professionals and patients.

Moreover, the mRS demonstrates concurrent validity by showing strong correlations with stroke-related measures, such as infarct volumes, and coherence with other stroke assessment tools [25] (Table 1).

Table 1. Modified Rankin scale [26].

	Modified Rankin Scale
0	No symptoms
1	No notable impairment in daily functioning. Capable of performing regular activities, even though some symptoms may persist.
2	Mild impairment: can manage personal affairs independently but cannot resume all prior activities.
3	Moderate impairment: needs assistance but can walk without help.
4	Moderate to severe impairment: Unable to attend to personal needs independently and cannot walk without assistance.
5	Severe impairment: requires continuous nursing care, bedridden, and incontinent.
6	Deceased.

The Medical Research Council (MRC) muscle strength scale is used to assess muscle strength across various medical conditions, including stroke.

It utilizes a sequence from 0 to 5, with each step representing a unique degree of muscle strength [27] (Table 2).

Table 2. Medical research council scale.

Medical Research Council (MRC) muscle strength scale	
0	No observable muscle contraction or movement.
1	Muscle contraction is evident, but there is no joint movement.
2	Muscles can move the joint when gravity is removed (passive movement).
3	Muscles can move the joint against gravity but not against additional resistance.
4	Muscles can move the joint against some resistance but are weaker than usual.
5	Normal muscle strength, enabling the joint to move against full resistance.

The NIHSS scale is a well-established tool for evaluating neurological impairments in stroke patients [28].

It comprises 15 individual items, covering various aspects of neurological function.

Each item is scored from 0 (normal) to a maximum of 2, 3, or 4, depending on the specific aspect being assessed [29].

The total NIHSS score provides a quantitative measure of stroke severity, with higher scores indicating more significant deficits [30] (Table 3).

Table 3. The National Institutes of Health Stroke Scale (NIHSS).

The National Institutes of Health Stroke Scale (NIHSS)		
Level of consciousness	0	Alert
	1	Not alert, arousable
	2	Not alert, obtunded
	3	Unresponsive
LOC questions	0	Answers both correctly
	1	Answers one correctly
	2	Incorrect
LOC commands	0	Obeys both correctly
	1	Obeys one correctly
	2	Incorrect
Gaze	0	Normal
	1	Partial gaze palsy
	2	Forced deviation
Visual fields	0	No visual loss
	1	Partial hemianopsia
	2	Complete hemianopsia
	3	Bilateral hemianopsia
Facial palsy	0	Normal
	1	Minor paralysis
	2	Partial paralysis
	3	Complete paralysis
Motor arm (A)Left; (B) Right	0	No drift
	1	Drift before 10s
	2	Falls before 10s
	3	No effort against gravity
	4	No movement
Motor leg (A)Left; (B) Right	0	No drift
	1	Drift before 10s
	2	Falls before 10s
	3	No effort against gravity
	4	No movement
Ataxia	0	Absent
	1	One limb
	2	Two limbs
Sensory	0	Normal
	1	Mild loss
	2	Severe loss
Language	0	Normal
	1	Mild aphasia
	2	Severe aphasia
	3	Mute or global aphasia
Dysarthria	0	Normal
	1	Mild
	2	Severe
Extinction/inattention	0	Normal
	1	Mild
	2	Severe

The Montreal Cognitive Assessment (MoCA) is a widely used screening tool designed to assess various cognitive functions and detect mild cognitive impairment.

The Montreal Cognitive Assessment (MoCA) evaluates cognitive abilities through tasks related to visuospatial skills, executive functions, language, memory, attention, and more, providing an overall cognitive assessment.

The total score on the MoCA provides an overall assessment of a person's cognitive abilities, with higher scores indicating better cognitive functioning [32].

Sample collection

Blood was collected after a fasting period, in the morning, by a skilled nurse.

Ethylenediaminetetraacetic acid (EDTA) tubes were used for sample collection.

The samples were then subjected to centrifugation, involving a spin at 3600 revolutions per minute (rpm) at 4°C for 10 minutes, utilizing an Eppendorf refrigerated centrifuge model 5417R.

This process led to the separation of plasma and red blood cell (RBC) fractions.

The samples were kept at -80°C until use, with precautions taken to prevent repeated thawing and freezing of the samples.

Ratio of neutrophils to lymphocytes-NLR

To determine neutrophils and lymphocytes in the blood samples, we employed standard venipuncture.

We quantified these populations using a flow cytometry apparatus (Abbott Diagnostics-CELL-DYN Ruby System).

The division was performed using the count of neutrophils and the count of lymphocytes. [33].

Statistical analysis

We conducted the statistical analysis using GraphPad software, specifically version 10.1.

For straightforward analysis, we utilized an unpaired t-test, while to evaluate the interaction between the investigated parameters and deficit scales, a Two-way ANOVA with Bonferroni correction was employed.

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Statistical significance was determined with p-values equal to or less than 0.05.

The data is presented as the mean value along with the standard error of the mean (SEM).

Results

Clinical and demographic characteristics of the cohort

The comparative analysis between the control and COVID groups has unveiled notable distinctions in multiple crucial variables.

The mean age of patients in COVID group was similar between the two groups, with a mean age of 72.87 years in the stroke-COVID group (ranging from 59 to 89), and an average age of 73 years (ranging from 53 to 87) in the control group.

Regarding gender distribution both groups featured a similar distribution.

Between the two groups there is a similar prevalence of certain medical conditions, including hypertension (96% for both groups), diabetes mellitus (26% vs. 32% in the control group), dyslipidemia (56% vs. 58% in the control group), and atrial fibrillation (30% vs. 28% in the control group).

Our objective included a comprehensive assessment of pulmonary involvement severity in both the control group and the Stroke-COVID group.

This evaluation focused on patients diagnosed with pneumonia, utilizing either X-ray or CT scan as diagnostic tools.

These findings are summarized in Table 4 for reference.

Table 4. The clinical and demographic information of the study participants.

Parameter	Control group	Stroke-COVID group	p-value
Age-mean years (interval)	73 (42-87)	72,87 (59-89)	0,7729
Sex: M(%)/F(%)	51,02/48,97%	42,5/57,5%	0.3697
High blood pressure, (%)	48 (96%)	48 (96%)	0,4423
Diabetes mellitus, (%)	16 (32%)	13 (26%)	0,3347
Dyslipidaemia, (%)	29 (58%)	28 (56%)	0,6296
Atrial fibrillation, (%)	14 (28%)	15 (30%)	0,8771
Pneumonia, (%)	26 (52%)	22 (52,38%)	0,862

Inflammatory response

We evaluated the inflammatory response by measuring several important markers, including the C-Reactive Protein (CRP), Fibrinogen, Neutrophil-to-Lymphocyte Ratio (NLR), and Erythrocyte Sedimentation Rate (ESR) (Figure1).

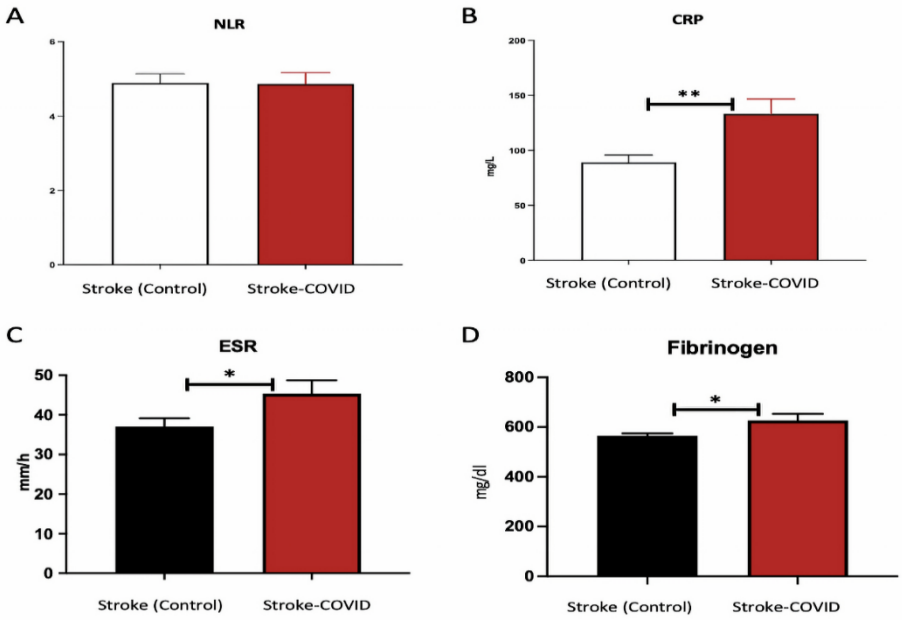

Figure 1. Illustrates the comparative findings for key inflammatory markers between the Stroke-COVID group and the control group. (A) The Neutrophil-to-Lymphocyte Ratio (NLR) was similar between the two groups (p=0.9532); (B) C-Reactive Protein (CRP) displayed a significant increment in the Stroke-COVID group (**p=0.0041); (C) Erythrocyte Sedimentation Rate (ESR) was significantly higher in the Stroke-COVID group compared to the control group (*p=0.0382); (D) Fibrinogen levels were significantly increased in the Stroke-COVID group (*p=0.0234).

The significant elevations in CRP (p=0.0041), ESR (p=0.0382), and Fibrinogen (p=0.0234) levels in the Stroke-COVID group collectively suggest that the co-occurrence of stroke and COVID-19 may result in a distinct inflammatory response, considering the combined impact of these two conditions on the inflammatory profile and overall health of the patients.

Coagulation function

Further investigations were carried out to assess coagulation function by examining the prothrombin time (PT) and international normalized ratio (INR) (Figure 2).

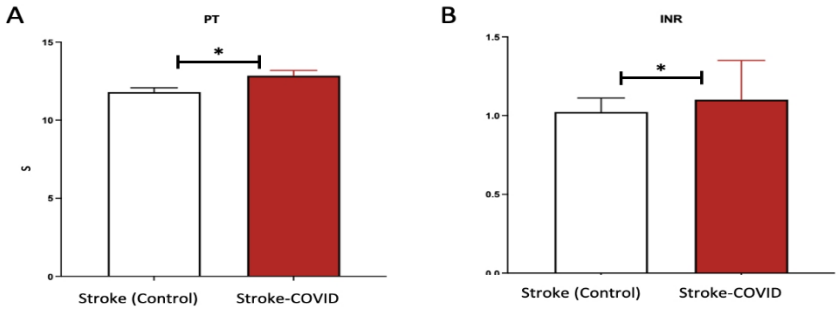

Figure 2. (A) Prothrombin time was significantly increased in the Stroke-COVID group (*p=0.0271) (B) The INR values demonstrated a similar trend, showing a significant difference between the Stroke-COVID group and the control group (*p=0.0433).

Our investigation into coagulation function revealed that individuals in the Stroke-COVID group had significantly elevated prothrombin time and INR values when compared to the control group.

Such changes in coagulation parameters may have implications for thrombotic risk and warrant close monitoring and appropriate interventions to mitigate potential complications.

Prognostic scales

We conducted an in-depth evaluation of the most critical prognostic scales that play a pivotal role in assessing the clinical status and outcomes of patients facing the dual challenges of stroke and COVID-19.

These scales include the National Institutes of Health Stroke Scale (NIHHS), Medical Research Council (MRC) scale, modified Rankin scale, and Montreal Cognitive Assessment scale (MoCA) (Figure 3).

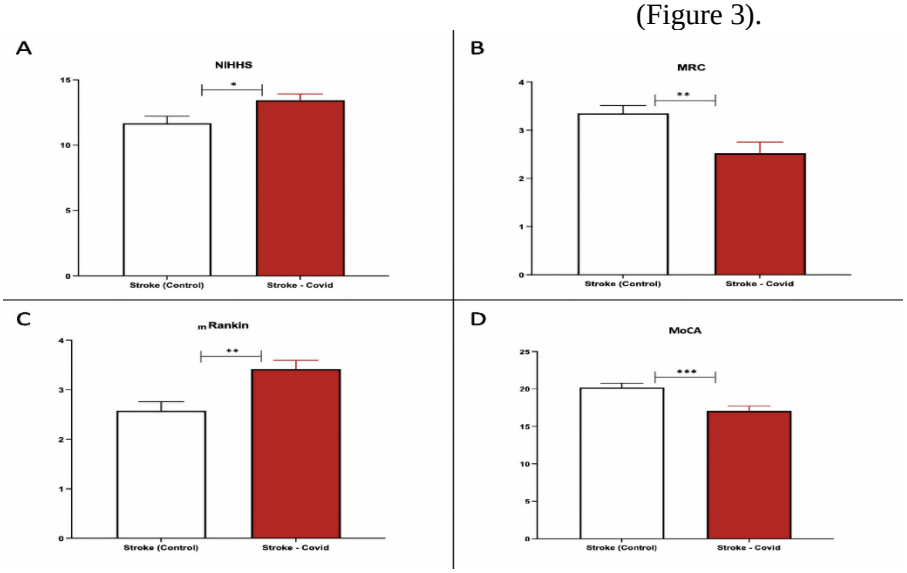

Figure 3. (A) The NIHHS scale exhibited a significantly higher value in the Stroke-COVID group (*p=0.0202); (B) The MRC score was associated with a worsened prognosis in the Stroke-COVID group (**p=0.0035); (C) The modified Rankin scale demonstrated a positive correlation with the Stroke-COVID group (**p=0.0023); (D) The Montreal Cognitive Assessment scale (MoCA) maintained the previously mentioned pattern (p=0.0007).***

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In summary, our assessment of these prognostic scales revealed significant differences between the Stroke-COVID group and the control group.

The Stroke-COVID group displayed higher scores on the NIHHS, indicating more severe neurological deficits.

Additionally, the MRC, modified Rankin scale, and MoCA scores were all indicative of a worse prognosis in the Stroke-COVID group.

Correlation of the prognostic scale

Additionally, our study aimed to explore the potential correlations between the NIHSS prognostic scale and key inflammatory factors (CRP and Fibrinogen), as well as the extent of pulmonary involvement in both groups.

We assessed pulmonary involvement by diagnosing pneumonia through the utilization of CT scans or X-rays as diagnostic methods.

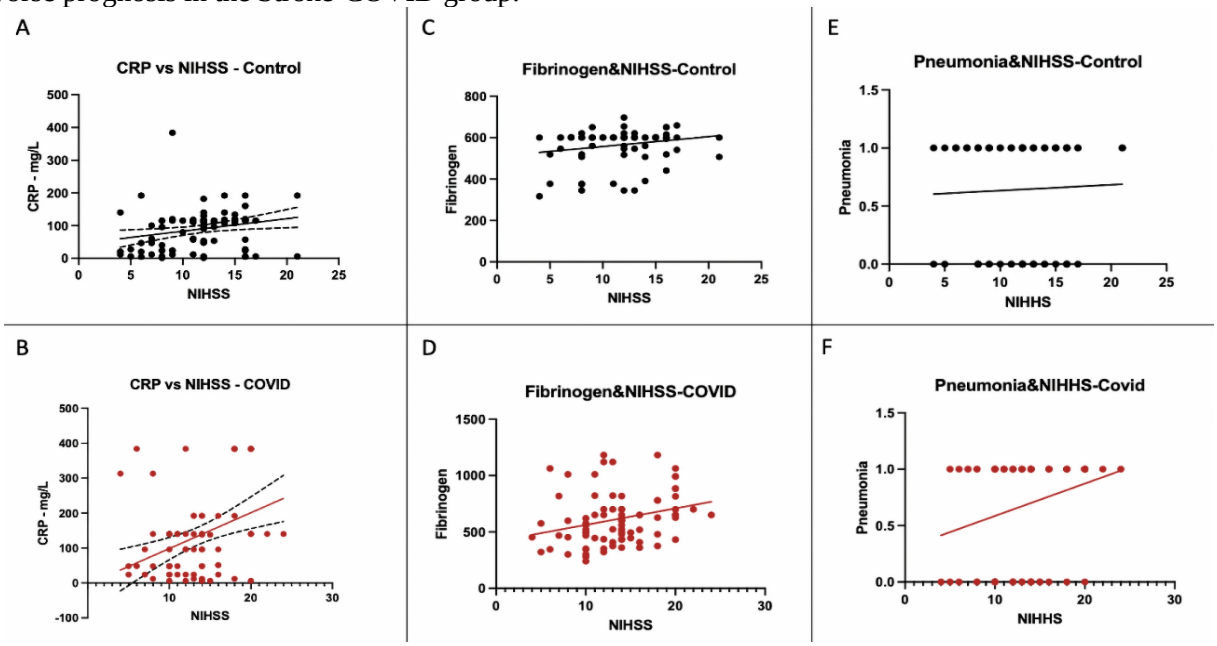

Figure 4. NIHSS score vs key inflammatory markers-C reactive protein (A) Control group (*p=0.0149), (B) Stroke-COVID group (p=0.007); Fibrinogen (C) Control group (p=0.0560), (D) Stroke-COVID group (*p=0.0106); and Pneumonia (E) Control group (p=0.7359), (F) Stroke-COVID group (*p=0.0141).***

In the control group, there was a statistically significant positive correlation between the NIHSS score and C-reactive protein (CRP) levels (*p=0.0149).

In the Stroke-COVID group, a similar positive correlation was observed between the NIHSS score and CRP levels (***p=0.007).

This suggests that as the NIHSS score increased, indicating more severe neurological deficits, CRP levels also tended to rise in both groups.

In the control group, the correlation between the NIHSS score and Fibrinogen levels did not reach statistical significance (p=0.0560).

However, in the Stroke-COVID group, a statistically significant positive correlation was found between the NIHSS score and Fibrinogen levels (*p=0.0106).

This implies that as the severity of neurological deficits increased, Fibrinogen levels also increased in this group.

When assessing the presence of pneumonia in the control group, there was no statistically significant correlation with the NIHSS score (p=0.7359).

In the Stroke-COVID group, a statistically significant positive correlation was observed between the NIHSS score and the presence of pneumonia (*p=0.0141).

This suggests that a higher NIHSS score, indicating more severe stroke-related deficits, is associated with a higher likelihood of pneumonia in individuals simultaneously dealing with COVID-19.

ROC investigation

Receiver operating characteristic curve is a powerful statistical technique employed to assess the effectiveness of a parameter in differentiating between groups.

Thus, we aimed to distinguish the group with acute ischemic stroke and pulmonary involvement from patients with ischemic stroke and concurrent COVID-19.

Our ROC analysis was performed for the examined inflammatory biomarkers and the NIHHS prognostic scale.

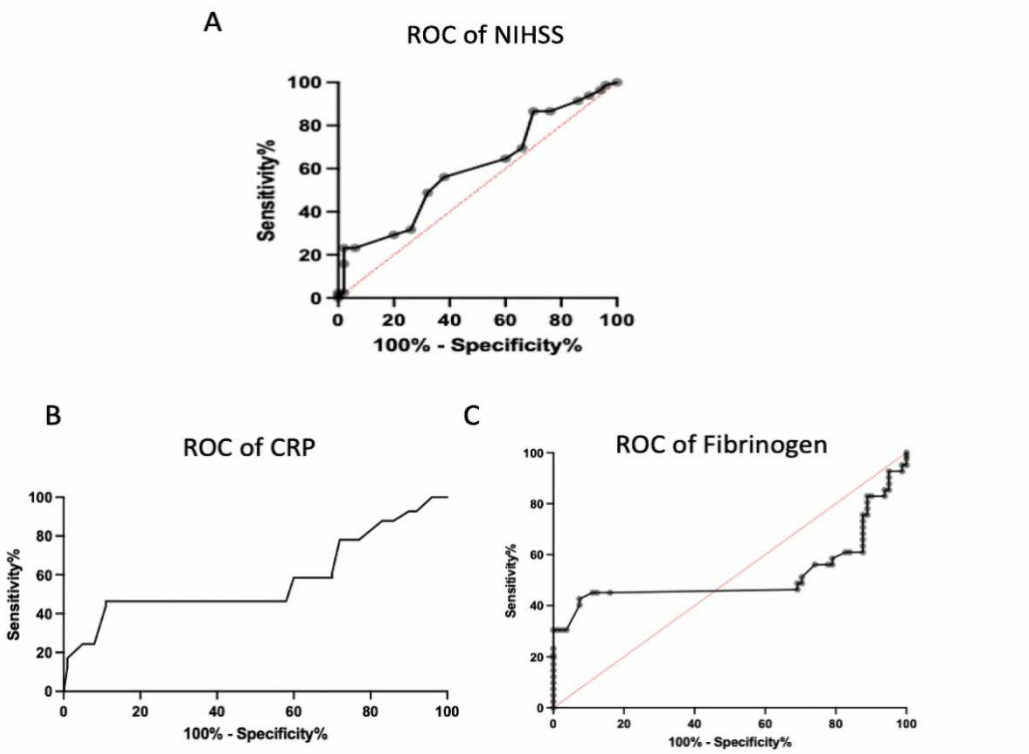

Figure 5. ROC analysis of (A) NIHSS (AUC: 0.600, 95% CI: 0.5168 to 0.6832, p=0.0204); (B) CRP (AUC: 0.5755, 95% CI: 0.4869 to 0.6641, p=0.0800); (C) Fibrinogen (AUC: 0.5184, 95% CI: 0.4206 to 0.6162, p=0.6843).

The ROC analysis for the NIHSS prognostic scale yielded an AUC of 0.600, suggesting that it demonstrates fair accuracy in distinguishing between patients with ischemic stroke and pulmonary involvement and patients with ischemic stroke and concurring COVID-19.

The p-value of 0.0204 indicates statistical significance, indicating that the NIHSS scale has some discriminatory power in this context. However, we obtained a poor discriminatory power for both CRP and fibrinogen, indicating limited accuracy in distinguishing between the groups.

Discussions

Acute ischemic stroke remains a significant global health challenge due to its multifaceted etiology and the ntricate clinical landscape it presents [1].

In parallel, the emergence of COVID-19, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has added a layer of complexity to the healthcare landscape [34,35].

Numerous studies have underscored the significance of inflammation, coagulation, and their intricate relationship in both acute ischemic stroke [36,37,38] and COVID-19 [39,40].

The interplay between these factors and their impact on pulmonary involvement, prognostic scales, correlations, and diagnostic accuracy through ROC analysis is a evolving and interesting field of investigation.

Our study delved into the intricate interplay among inflammation, coagulation, pulmonary implications, and prognostic evaluations in individuals experiencing acute ischemic stroke alongside a concurrent COVID-19 infection.

Several critical insights emerge from our analysis, providing valuable contributions to the evolving understanding of these intricate dynamics.

Firstly, the study revealed that patients with acute ischemic stroke and concurrent COVID-19 infection exhibited significant elevations in key inflammatory markers, including C-Reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR), compared to those with acute ischemic stroke alone.

This suggests that the co-occurrence of stroke and COVID-19 leads to a distinct and more pronounced inflammatory response, findings that are similar to what is known in the literature [41,42].

Secondly, individuals in the group with both acute ischemic stroke and COVID-19 showed significantly elevated prothrombin time (PT) and

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international normalized ratio (INR) values when compared to the control group.

These findings indicate alterations in coagulation parameters, which may have implications for thrombotic risk and patient management, as previously highlighted in the literature [43,44].

Moreover, we demonstrated that patients in the acute ischemic stroke and COVID-19 group had higher scores on the National Institutes of Health Stroke Scale (NIHSS), indicating more severe neurological deficits.

Additionally, the Medical Research Council (MRC) scale, modified Rankin scale, and Montreal Cognitive Assessment scale (MoCA) scores were indicative of a worse prognosis in the group with both conditions.

Nannoni S et al. reaffirmed these observations and points toward a distinct pattern of strokes associated with COVID-19, characterized by severe National Institutes of Health Stroke Scale (NIHSS) scores and unfavorable outcomes [45].

The research identified positive correlations between the NIHSS score and CRP levels in both the control group and the group with acute ischemic stroke and COVID-19, suggesting that as neurological deficits became more severe, CRP levels tended to rise.

A similar correlation was found between the NIHSS score and Fibrinogen levels in the group with both stroke and COVID infection.

The ROC analysis indicated that the NIHSS prognostic scale has fair accuracy in distinguishing between patients with ischemic stroke and pulmonary involvement and patients with ischemic stroke and coronavirus.

However, both CRP and Fibrinogen displayed limited accuracy in this regard.

These findings collectively highlight the complex and interrelated dynamics of inflammation, coagulation, prognostic assessments, and diagnostic accuracy in the context of acute ischemic stroke and concurrent COVID-19 infection.

They provide valuable insights for clinical management and patient care in these complex scenarios.

Conclusion

In summary, our comprehensive investigation unravels the intricate and multifaceted interplay involving inflammation, coagulation, pulmonary involvement, prognostic scales, and the presence of COVID-19 within the context of acute ischemic stroke.

These findings not only provide essential insights but also emphasize the urgent necessity for a more profound understanding of the underlying mechanisms at play and the potential implications of COVID-19 on the presentation and outcomes of stroke.

Our research reveals that the relationship between stroke and COVID-19 is characterized by complexity, as it encompasses a myriad of contributing factors.

This dynamic interplay necessitates further in-depth exploration to elucidate causative elements and gain a comprehensive understanding of the repercussions of this synergy.

Such knowledge is imperative for the development of more efficacious strategies for the management and intervention of patients confronted with the dual challenges posed by stroke and COVID-19.

Study limitations

The study may have a relatively small sample size, which could affect the generalizability of the findings to larger populations.

A larger and more diverse sample could provide a more comprehensive understanding of the relationships studied.

The study was conducted in a single center, which might limit the generalizability of the results to broader geographic or healthcare settings.

Multi-center studies could provide a more representative picture of the population.

While efforts have been made to control for confounding variables, there may still be unaccounted factors that could influence the observed outcomes.

Future research with more comprehensive control of confounders may provide more definitive results.

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Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of University of Medicine and Pharmacy of Craiova (no. 202/19.10.2022).

Conflicts of Interest

The authors declare no conflict of interest.

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