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Prognosis of the post COVID-19 stroke based on D-dimer and inflammatory markers: A mixed model meta-regression analysis

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Abstract

Background & Objective: With regard to the importance of inflammatory biomarker and stroke in COVID-19 prognosis, this study aims to compare the mortality of stroke in COVID-19 patients based on the level of inflammatory biomarkers, considering the temporality of stroke occurrence after COVID-19 infection. *Methods:* As a secondary study, aggregate data were collected by a systematic review. Mixed model meta-regression analyses were conducted to study the effects of stroke, inflammatory biomarkers and D-dimer on mortality of patient with COVID-19 as main effects and interactions. The effect measure was death rate. The protocol was registered in PROSPERO with registration number CRD42023383065. *Results:* A total of 2,725 COVID-19 patients, consisting of 96 patients with stroke with a temporal precedence of COVID-19 were investigated from three studies. Among the inflammatory biomarkers, only CRP found eligible for pooled analysis. In the interaction model of CRP, significant positive interactions with CRP were found for both groups of stroke and non-stroke ($P < 0.001$), in which the interaction with stroke group was more severe. In the interaction model of D-dimer, a significant positive interaction with D-dimer was found for the stroke group ($P < 0.001$), while the interaction with the non-stroke group was not statistically significant ($P = 0.158$). *Conclusion:* The present study found the role CRP and D-dimer in prognosis of stroke in patients with COVID-19 as both main effect and interaction modeling. The evidence obtained from these mixed model meta-regression analyses was of moderate quality.

Keywords: Systematic review, meta-analysis, statistical modeling, COVID-19, stroke, D-dimer, inflammatory markers

INTRODUCTION

The coronavirus disease 2019 (COVID-19) was recognized at the end of 2019. It was caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The World Health Organization (WHO) proclaimed COVID-19 a global pandemic in March 2020.[1] Despite being classified as a severe acute respiratory syndrome, there were many reports of COVID-19 patients experiencing a range of clinical manifestations involving stroke.[2]

Stroke was reported as an important neurovascular and one of the most disabling complications of COVID-19.[3,4] Patients who suffer from ischemic stroke demonstrate poor prognosis. In a study of hospitalized patients for ischemic stroke between 2003 and 2019, hospital fatality was 9.1 %, 30-day mortality was 14.2 %, and 1-year mortality was 28.4%.[5]

A systematic review reported that ischemic stroke accounted for 87.5% of neurological involvement in COVID-19 patients.[6] Another review, focusing on 214 COVID-19 patients, found that severe infections were associated with a higher probability of neurological manifestation, such as acute strokes.[7] Currently, COVID-19 is considered an independent risk factor for acute ischemic stroke.[8] Moreover, stroke has an important effect on the final outcome of COVID-19 patients[9], making acute ischemic stroke a vital contributor to mortality and morbidity in COVID-19 patients.[10]

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In a systematic review, it was noted that COVID-19 patients show elevated levels of D-dimer, C-reactive protein (CRP) and Erythrocyte Sedimentation Rate (ESR). It is known that COVID-19 infection can increase the risk of thrombosis due to prothrombotic factors from high D-dimer titters.[11] Another systematic review and meta-analysis revealed a significant relationship between COVID-19 severity and raised levels of CRP and D-dimer.[12] Furthermore, investigations have indicated that C-reactive protein (CRP) significantly affects ischemic stroke and COVID-19 prognosis[13,14] and could serve as a screening tool for symptomatic patients.[15] The notable elevation of CRP and D-dimer levels, as inflammatory markers in COVID-19 patients, has been associated with an increased risk of ischemic stroke.[16] A case-based systematic review involving 87 patients demonstrated that higher levels of CRP, D-dimer and ESR were related to poor prognosis in COVID-19 patients.[4] Additionally, a meta-analysis with 3962 COVID-19 patients highlighted a positive correlation between inflammatory biomarkers such as CRP and ESR, with COVID-19 severity, complication, and mortality.[17]

However, previous prognosis studies did not assess the prognostic role of biomarkers in COVID-19 patient affected by stroke in comparison with non-stroke COVID-19 patients. With regard to importance of inflammatory biomarker and stroke in COVID-19 prognosis, this study aims to compare the mortality of stroke in COVID-19 patients based on the level of inflammatory biomarkers, taking account of the temporal relationship of stroke occurrence after COVID-19 infection.

METHODS

Study design

The present mixed model meta-regression analysis was conducted according to Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement. The protocol of this study was registered in PROSPERO with registration number CRD42023383065.

Search Strategy

A systematic search was performed in PubMed, Scopus, Web of Science and Google Scholar from 2018 December to 2022 August 15th. The combined search terms were used is : ("COVID 19" OR "SARS CoV 2 Infection" OR "Coronavirus Disease 2019" OR "COVID 19 Virus Disease" OR "2019 nCoV Infection" OR "COVID 19 Pandemic" OR "hospitalized COVID19" OR "non- hospitalized COVID19") AND ("inflammatory parameters" OR "biomarkers" OR "Biological Marker" OR "Immune Markers" OR "Serum Markers" OR "Surrogate End Points" OR "Clinical Markers" OR "Viral Markers" OR "Biochemical Marker" OR "Laboratory Markers" OR "Inflammation Mediators" OR "immune-inflammatory parameters") AND ("Cerebrovascular Stroke" OR "Stroke" OR "Cerebral Stroke" OR "Acute Stroke" OR "Ischemic Strokes" OR "Acute Ischemic Stroke" OR " Transient Ischemic Attack). In addition to systematic search, a manual search was done to include relevant missing study in our study.

Selection criteria (inclusion & exclusion criteria)

Although there were no location restrictions, certain studies were excluded such as non-observational, non-English publications, and animal studies. In the included studies, the COVID-19 patients should be categorized into two groups: those with stroke and those without stoke, with confirmed temporality between COVID-19 and stroke events. The main outcome examined in this study was the mortality of ischemic stroke in COVID-19 and non-COVID-19 patients. Inflammatory biomarkers were used as comparators.

Screening and study selection process

First, all references were checked for the elimination of duplicates. Two independent authors performed eligibility screening for all search results in two steps: in the first step, titles and abstracts were checked, and in the second step, the full-text articles of selected items were assessed for eligibility. Disagreements were resolved through agreement after discussion.

Data extraction

The data included age, sex, comorbidity such as diabetes, hypertension and heart disease, as well as inflammatory biomarkers such as D-dimer, ESR, BUN, Cr, along with mortality. Data were collected from two authors to uniform Microsoft Excel sheet. The accuracy of the data was checked and confirmed. Disagreements were resolved through discussion.

Risk of bias assessment (quality assessment)

The Newcastle-Ottawa score (NOS) was used to

assess the quality and risk of bias of the included studies. NOS is a scoring system based on three domains: the selection of the study sample, comparability of the studies, and assessment of outcomes.

Data analysis and evidence synthesis

We employed a quantitative strategy for data synthesis, focusing on reporting the percentage of mortality divided into two groups: those with stroke and those without stroke. Additionally, we analysed inflammatory biomarkers such as ESR and CRP. We utilized the multi-level mixed effect linear regression method to identify pooled effects. In this approach, the outcome was mortality, prognostic factors included stroke, inflammatory biomarkers, and demographic variables, while the random effect variable was study ID. The random part of the model consisted of the random intercept of study IDs, with no random slope applied. Furthermore, a weight was assigned to each study ID, calculated by the inverse of mortality percentage variance. Heterogeneities were assessed using the Cochran Q test and I^2, along with reporting the random variance of study IDs. Data analysis was conducted using Stata 14 software (Stata Corp. LLC, TX, US). Sensitivity analysis was also considered. Grading of Recommendation, Assessment, Development and Evaluation (GRADE) tool was used to investigate quality and certainty of evidence.

RESULTS

PRISMA flowchart

The initial database search yielded 720 records (PubMed = 72, Scopus = 449, Web of Sciences = 77, Google Scholar = 122) with 143 duplicate studies subsequently excluded. After title and abstract screening, 516 studies were excluded, leaving 61 studies. Additionally, four studies were added through manual search in other sources. All the remaining studies were assessed by full-text screening based on the eligibility criteria. Finally, three studies were eligible to be included in our analysis.[3,9,18]

Baseline characteristics

In our analysis, we included three studies with total population of 2,725 COVID-19 patients, consisting of 96 patients with stroke (stroke group) and 2629 patients without stroke (non-stroke group), with a temporal precedence of COVID-19. Two studies were conducted in China and another in India. The weight of studies was calculated based on logit-transformed inverse variance weighting (IVW) of death rates, and the sum of weights was obtained 200. Quality assessment using NOS demonstrated that with regard to selection, comparability and outcome, the studies had good quality with seven scores and they did not show a risk of bias. In stroke group patients, the percentage range for male, age above 60 years, diabetes mellitus, and hypertension were 54.5 – 76.7, 61.7 – 92.0, 28.0 – 54.5 and 56.7 – 81.8, respectively. In non-stroke group patients, these parameters were 39.9 – 73.3, 37.0 – 65.0, 12.0 – 35.0 and 22.1 – 35.0, respectively. Among the blood markers, ESR was investigated in only one study, and no study investigated procalcitonin. Therefore, we considered only CRP and D-dimer for meta-analysis (Table 1).

Pooled analysis

Associations of CRP and D-dimer with stroke were studied using the mean difference (MD) effect measure. Accordingly, CRP showed a trend for significance, being lower in non-stroke group (MD = -15.27 mg/L, 95% CI: -40.39 – 9.84, I^2 >50%, random effects model). Similarly, D-dimer also demonstrated a trend for significance, being lower in non-stroke group (MD = -1.74 mg/L, 95% CI: -3.99 – 0.50, I^2 >50%, random effects model) (Figure 1). Pooled death rates were calculated for each stroke and non-stroke groups, resulting in a pooled death rate of 0.07 (95% CI: 0.07 – 0.09) in the non-stroke group and 0.47 (95% CI: 0.37 – 0.58) in the stroke group. Since the common effect weights were needed for mixed model meta-regression analysis, we utilized the common effect model to report pooled death rate (also, I^2 was not significantly more than 50% in the non-stroke group) (Figure 2).

Publication bias

Funnel plot was used to investigate publication bias based on pooled effects from Figure 2. Accordingly, all the studies were inside the funnel for the non-stroke group. In the stroke group, the study of Yao *et al*.[18] was outside the funnel, showing a significantly lower effect size (Figure 3).

Mixed model meta-regression

Death rate of the studies was predicted using multilevel mixed effects model meta-regression

Table 1: Baseline characteristics of the studies

Study (country)	Group	Male %	Age>60 %	DM %	HTN %	CRP mean	D-dimer mean	ESR mean	Sample size	Death rate	Weight	NOS
Goyal (India)[9]	Stroke	76.7%	61.7%	53.3%	56.7%	26.7	1.5	25.5	60	0.567	14.7	3+3+3
	Non-stroke	73.3%	65.0%	35.0%	35.0%	9.9	0.3	20.0	60	0.133	6.9	
Yao (China)[18]	Stroke	64.0%	92.0%	28.0%	68.0%	33.8	1.8		25	0.160	3.4	3+3+3
	Non-stroke	49.6%	52.6%	13.6%	28.2%	47.5	2.8		2361	0.070	153.5	
Li (China)[3]	Stroke	54.5%	90.9%	54.5%	81.8%	57.9	8.5		11	0.455	2.7	3+3+3
	Non-stroke	39.9%	37.0%	12.0%	22.1%	12.1	0.5		208	0.102	19.0	
Mean									454.17		33.4	
Total									2725		200	

DM: diabetes mellitus. HTN: hypertension. NOS: Newcastle Ottawa scale subdomains including selection, comparability and outcome from left to right.

to generalize the regression coefficients to undone putative studies. Since study variations were considered for random intercept of the models, common effect weights were used. Due to the low number of studies and saturation of the degrees of freedom, the serum markers were imported to the models one by one (and also to prevent collinearity of the markers).

In the CRP model, one unit increase in CRP was associated with about 0.5% lower death rate in a putative study (P <0.001), adjusted with the stroke group. In the D-dimer model, one unit increase in CRP was associated with about 1.9% lower death rate in a putative study (P <0.001), adjusted with the stroke group.

In addition to the mentioned models, interactions between groups and serum markers were studied. In the interaction model of CRP, significant positive interactions with CRP were found for both groups (P <0.001), in which the interaction with stroke group was more severe. In the interaction model of D-dimer, a significant positive interaction with D-dimer was found for the stroke group (P <0.001), while the interaction with the non-stroke group was not statistically significant (P =0.158) (Table 2, Figure 4).

Sensitivity analysis

Due to the different effect direction of Yao's study[18], a sensitivity analysis was conducted using this scenario that the mean of CRP and D-dimer would be exchanged in the stroke and non-stroke groups. Subsequently, all four multilevel modeling analyses were conducted with this scenario. Accordingly, all beta coefficients of the four models were significantly positive (P <0.001). These results were consistent with those in Table 2, except for the interaction model of D-dimer in the non-stroke group, where the coefficient was positive and significant in the generated scenario, while it was negative and non-significant in the base scenario (not shown as table).

Certainty of evidence

According to GRADE tools, the evidence for the pooled association of the biomarkers with stroke was rated as "very low quality". The evidence for pooled death rates was rated as "low quality", and the evidence for mixed modeling was rated as "medium quality" (Table 3).

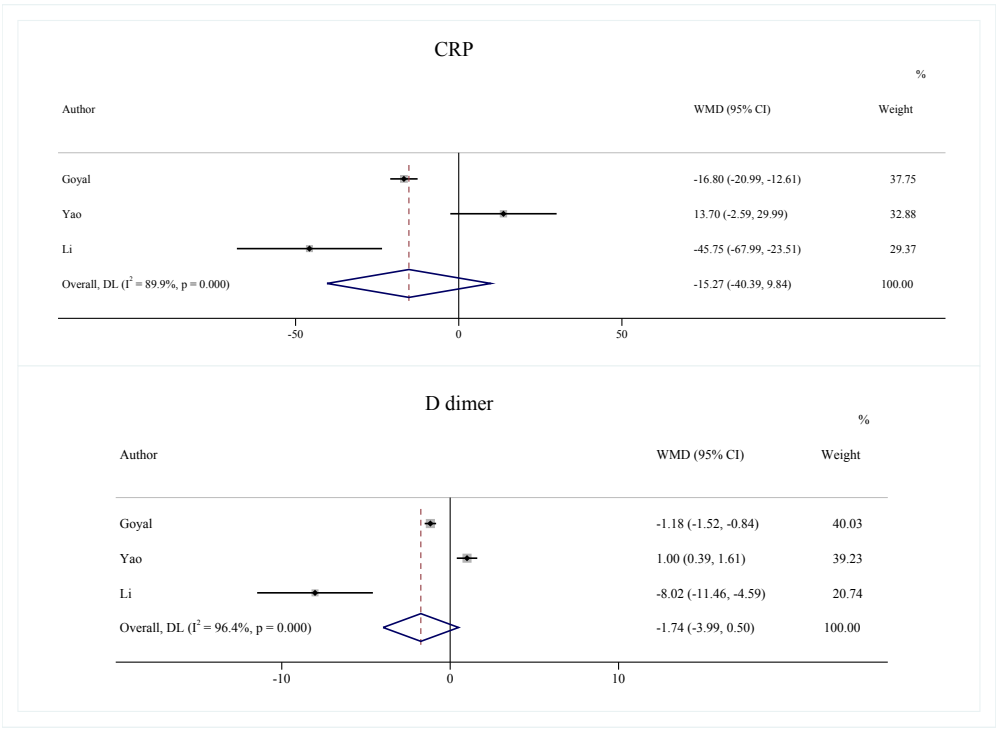

Figure 1. Forest plot to compare mean difference of CRP and D dimer between stroke and non-stroke groups. Negative effect sizes indicate lower mean in non-stroke group.

WMD: weighted mean difference.

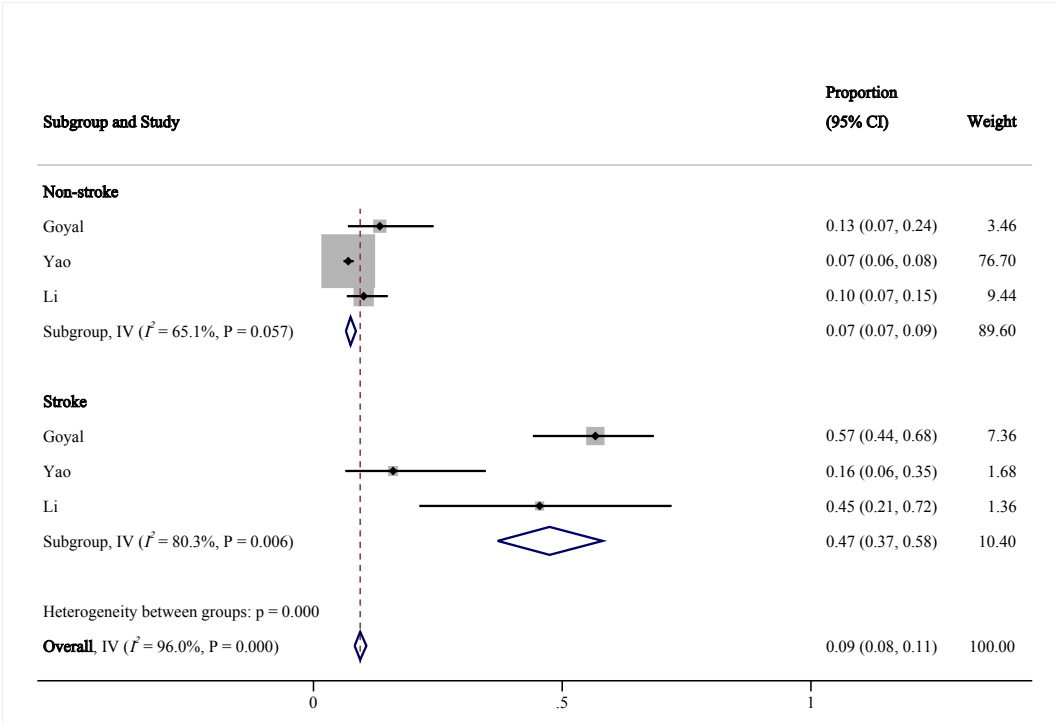

Figure 2. Forest plot to reach pooled death rate in stroke and non-stroke groups.

IV: inverse variance weighted.

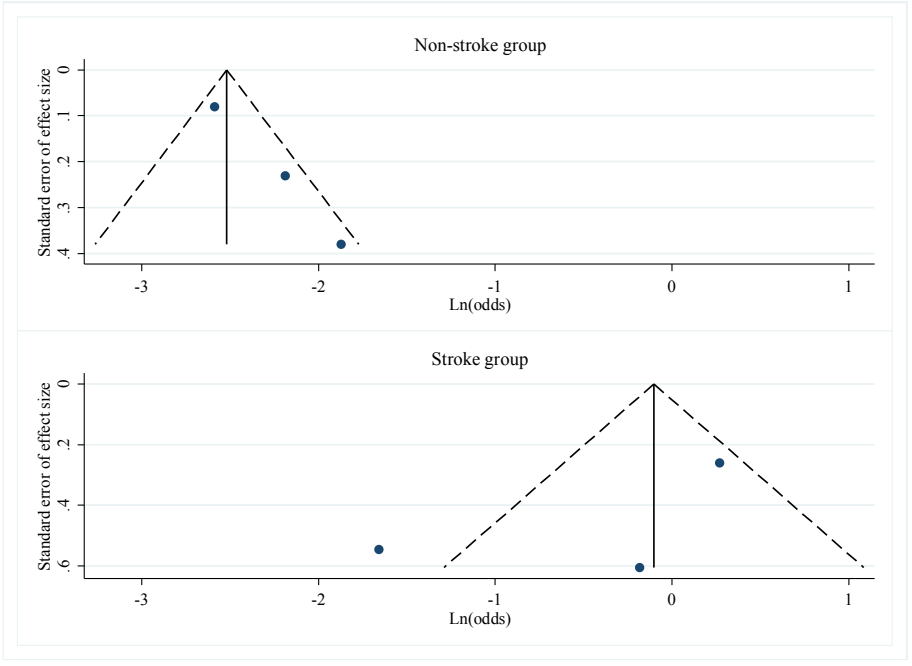

Figure 3. Funnel plot (95% CI) to show distribution of effect sizes (death rates).

Table 2: Multilevel mixed effects modeling to study the effects of CRP and D-dimer on death rate

Model	Predictors	Coefficients	Standard error	Z value	P value	95% CI (Lower, upper)		AIC	BIC
CRP								-890.0	-883.5
	Stroke	0.238	0.009	27.49	<0.001	0.221	0.255		
	CRP	0.005	0.000	14.88	<0.001	0.004	0.006		
	Constant	0.006	0.083	0.08	0.937	-0.147	0.160		
	Random part								
	Var (Constant)	0.018	0.000			0.004	0.006		
	Var (Residual)	0.006	0.000			0.000	0.001		
D-dimer								-794.5	-778.1
	Stroke	0.268	0.011	23.84	<0.001	0.245	0.290		
	D dimer	0.019	0.003	6.70	<0.001	0.013	0.024		
	Constant	0.107	0.051	2.10	0.036	0.007	0.206		
	Random part								
	Var (Constant)	0.008	0.006			0.002	0.039		
	Var (Residual)	0.001	0.000			0.001	0.001		
CRP # Group								-712.7	-696.2
	Non-stroke	0.004	0.001	7.17	<0.001	0.003	0.006		
	Stroke	0.010	0.000	21.80	<0.001	0.009	0.011		
	Constant	0.041	0.090	0.45	0.650	-0.135	0.216		
	Random part								
	Var (Constant)	0.023	0.019			0.005	0.118		
	Var (Residual)	0.001	0.000			0.001	0.002		
D-dimer # Group								-563.9	-547.4
	Non-stroke	-0.016	0.011	-1.41	0.158	-0.039	0.006		
	Stroke	0.053	0.004	12.25	<0.001	0.045	0.062		
	Constant	0.195	0.075	2.61	0.009	0.048	0.342		
	Random part								
	Var (Constant)	0.016	0.013			0.003	0.082		
	Var (Residual)	0.003	0.000			0.003	0.004		

AIC: Akaike information criterion. BIC: Bayesian information criterion. Var: variance. # Interaction sign.

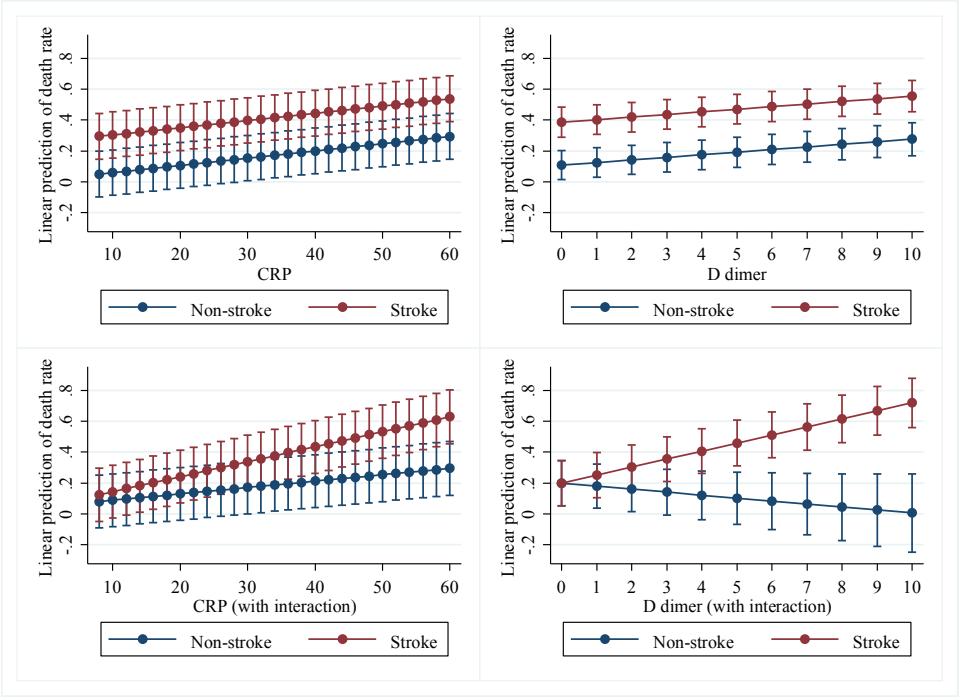

Figure 4. Marginal prediction of multilevel mixed effects modeling for prediction of death rate based on Table 2. The error bars indicate 95% CI.

DISCUSSION

Interpretation

This study aimed to find a marker to predict stroke in COVID-19 patients, preferably assessing stroke prognosis independently of COVID-19 prognosis, necessitating consideration of temporal precedence. Due to the strictness of eligibility criteria, only three studies were selected, that their quality assessment received full score. Our meta-analysis included an acceptable population since it is difficult to gather 96 stroke patients at an individual level in studies confirmed by temporal precedence of COVID-19. To avoid overpowering the results, we used the method of weighted studies to reduce the sample size from 2,725 to 200 at the individual level. Comparing the range of hypertension (HTN), diabetes mellitus (DM), age above 60 years and male patients in the stroke group to the non-stroke group, HTN ranges did not overlap and the HTN range of stroke group was higher. The ranges of DM and age above 60 years had some overlap, but the stroke group had more level range. Male ranges almost overlapped. Based on a non-parametric approach, blood pressure appeared to have an effective role in the occurrence of stroke.

As expected, the results of the pooled analysis demonstrated that the mortality rate of COVID-19 in stroke group was higher than in non-stroke group. Additionally, the difference in CRP and D-dimer ranges between stroke and non-stroke group was expectable.

Based on the funnel plot, the study of Yao *et al*.[18] reported results that did not conform to the other results. Likely, this difference originated from reporting two-centered results. Despite the lower average in the stroke group, stroke group with D-dimer levels over 0.5 mg/L and CRP levels over 1 mg/L had a higher percentage of patients than the non-stroke group. In any case, this study, with a high weight, played a modifying role in adjusting the exaggerated results of the other two studies.

In multi-level modeling, because death rate, as an outcome is presented as aggregated data and measured effect, it is named meta-regression instead of regression. The regression coefficients of the results, assuming multiple putative studies, demonstrate how the mortality rate differs with each unit of difference in the average marker.

Both CRP and D-dimer showed a positive coefficient in predicting the outcome, indicating their prognostic role regardless of the presence of stroke. However, this study aimed to identify

Table 3: GRADE of evidence

Outcome	GRADE criteria	Rating	Footnotes	Quality of evidence
Pooled analysis (association of groups with CRP and d-dimer)	Risk of bias	0	According to NOS	Very low
	Inconsistency	1-	Presence of heterogeneity	
	Indirectness	0	No concern regarding PICO	
	Impression	1-	Wide 95% CI	
	Publication bias	1-	Different effect direction of one study	
	Large effect	0	Not statistically significant	
	Dose response	0	Not applicable	
	No plausible confounding	0	Effects of underlying diseases not controlled	
Pooled analysis (death rate)	Risk of bias	0	According to NOS	Low
	Inconsistency	1-	Presence of heterogeneity	
	Indirectness	0	No concern regarding PICO	
	Impression	0	No wide 95% CI in non-stroke group	
	Publication bias	0	Funnel plot was approximately OK	
	Large effect	1+	Huge difference in subgroup death rates	
	Dose response	0	Not applicable	
	No plausible confounding	0	Effects of underlying diseases not controlled	
Mixed models	Risk of bias	0	According to NOS	Moderate
	Inconsistency	0	Heterogeneity controlled by random intercept	
	Indirectness	0	No concern regarding PICO	
	Impression	0	Narrow 95% CI	
	Publication bias	0	No considerable change in sensitivity analysis	
	Large effect	1+	Clinically significant coefficients	
	Dose response	0	Not applicable	
	No plausible confounding	0	Effects of underlying diseases not controlled	

a more prominent prognostic marker within the stroke group. Consequently, interactions between groups and markers were analyzed. Both markers showed a positive significant interaction with the stroke group, but with a notable difference: CRP emerged as a more accurate prognostic marker, whereas, D-dimer was more distinctive in differentiating mortality rates between stroke and non-stroke patients. Specifically, D-dimer level greater than or equal to 5 mg/L distinguished the confidence interval of the outcome in the stroke group from the non-stroke group.

A recent systematic review and meta-analysis demonstrated a higher mortality rate of COVID-19 patients with stroke compared to those without stroke, with a risk difference of 24% (95% CI: 0.10-0.39; p = 0.001). Notably, this study established the confirmed temporality between COVID-19 and stroke and revealed a difference in certain markers between the two groups. However, it did not assess the role of inflammatory biomarkers as prognostic factors for mortality.[19] Compared with our study, they found 24% increase in risk of mortality, while we found 40% increase in risk of mortality. However, our evidence in this regard was low quality according to GRADE.

Another meta-analysis study evaluated mortality risk associated with elevated CRP and D-dimer levels in COVID-19 patients. The statistical analysis showed a six-fold elevation of CRP and D-dimer in severe COVID-19 cases. The study identified high levels of CRP at 10 mg/L and above and high levels of D-dimer at 0.5 mg/L and above, as indicators of severe conditions.[16] On the

other hand, the present study aimed to study the additive effect of stroke on these biomarkers in COVID-19 patients. Hence, interaction analysis was used.

In another systematic review and meta-analysis that included 183 patients with COVID-19 and stroke, the frequency and prognosis of stroke were evaluated. However, this study did not, consider temporality between COVID-19 and stroke. The frequency of stroke in hospitalized COVID-19 patients was 1.1% (95% confidential interval [CI]: 0.6–1.6), and it was associated with older ages. A high level of D-dimer at 3.3 mg/L (95% CI: 1.7–4.9), was associated with higher mortality.[20] In a systematic review and meta-analysis assessing the relationship between biomarkers and the prognosis of COVID-19 patients, a significant association was found between high levels of CRP (4.37, 95% CI: 3.37–5.68), D-dimer (3.39, 95% CI: 2.66–4.33), and COVID-19 severity.[12] Another meta-analysis study indicated that higher levels of D-dimer (2.24, 95% CI: 0.84–3.64) might be associated with poor prognosis in COVID-19 patients.[21]

Due to generalizing of aggregated data results to individual level, ecological fallacy was one of the limitations of this study. However, this study collected results of a certain COVID-19 population, affected by stroke. Additionally, a multilevel mixed effects method was used to account for the heterogeneity effect of studies as a random intercept. As a result, this approach lessened the impact of heterogeneity on the estimated relationships.

In conclusion, the present study found the role CRP and D-dimer in prognosis of stroke in patients with COVID-19 as both main effect and interaction modeling. The evidence obtained from these mixed model meta-regression analyses was moderate quality. Therefore, future studies should be conducted with multicenter and prospective design to increase the quality of evidence.

DISCLOSURE

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Conflicts of interest: None

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