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D-dimer to fibrinogen ratio as a marker for acute cerebral venous thrombosis

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Abstract

Despite D-dimer to fibrinogen ratio (DFR) being reported as a prognostic factor for cerebral venous thrombosis (CVT), we note some concerns about the misused terminology (prognostic versus predictive), potential variability in D-dimer and fibrinogen assays that may impact the reliability and utility of DFR. From the statistical aspect, its validity was not adequately ensured due to inappropriate methods (inability to address multicollinearity, confounding, and multiple comparisons) and lack of validation for unvalidated discrimination cut-offs. The prognostic value of DFR was not clinically or statistically justified, given its poor-to-acceptable discrimination. Finally, an unexpectedly positive association between venous cerebral infarction and non-severe CVT suggests possible issues in data labelling, reference value, uncontrolled confounders/biases, or overadjustment. Addressing these issues would strengthen the reliability, validity, and utility of DFR in CVT prognosis.

Keywords D-dimer, Fibrinogen, Venous thromboembolism, Cerebral venous thrombosis

To the Editor,

We read with great interest, and we would like to congratulate Lan et al. on their study entitled "A retrospective cohort study on a novel marker to predict the severity and prognosis of acute cerebral venous thrombosis: D-dimer to fibrinogen ratio," published in the Thrombosis Journal [1]. Their results provide significant implications regarding the prognostic values of the D-dimer to fibrinogen ratio (DFR), underscoring the importance of considering the DFR as a novel marker for cerebral venous thrombosis (CVT). However, we have some comments about the design, statistical analysis, and data interpretation/reporting of their study that the authors did not mention or address. We believe the following considerations could support a more robust evaluation of DFR's reliability, validity, and utility in CVT, offering further insight into its potential role as a prognostic tool in clinical practice.

For the study design, due to the challenge in determining the temporal association between DFR and the severity of CVT, it is highly likely that the term "predictive" has been misused in this study from a medical context. A more appropriate term is "prognostic". Generally, a prognostic factor provides information about a patient's overall outcome for a disease process, whereas a predictive factor provides information about how a patient may respond to a specific therapy [2]. Although having different implications, these might have been used interchangeably in this study. This mistake can easily mislead people without statistical or epidemiological backgrounds, as these terms serve different purposes in research and clinical practice [2]. In this case, misinterpreting DFR as a predictive factor may encourage the use of this marker in guiding CVT treatments, while there is no evidence supporting such practice. Additionally, the authors did not address the potential variability in

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D-dimer and fibrinogen measurements across patients, especially over an extensive timeframe (from 2010 to 2023). Any changes in laboratory practices or assay sensitivity could have introduced variability in DFR values, potentially impacting the findings.

For the statistical analysis, the authors seemed to neglect the fact that multicollinearity, a situation where ≥ 2 independent variables in a model are highly correlated, is an extreme case of confounding [3]. Correlation analysis has never been a standard approach to identify nearly collinear variables, as it cannot estimate the measures of collinearity, e.g., tolerance or variance inflation factor. This suggested that some potentially confounding variables had been excluded from the regression models and not been adjusted for, leading to a high risk of biased coefficient estimates. Bonferroni correction was also not applied correctly. The authors only pre-specified 3 primary statistical tests (0.05/3), but multiple comparisons were conducted (with > 3 p-values being reported). This may still introduce the risk of false positives (or inflated type I error). Another concern is the lack of validation analysis, where unestablished discrimination cut-offs of DFR identified through the receiver operating characteristic curve (ROC) should be internally and externally validated to ensure the generalisability of the findings [4]. Given the challenge of conducting this externally, internal validation, at least, should have been performed to provide more evidence for DFR applicability. In case of small sample size, the following methods can be considered for interval validation: bootstrapping, leave-one-out cross-validation, k-fold cross-validations with repeats.

For the data interpretation/reporting, while DFR was found to be associated with the severity and clinical outcomes of CVT, the authors did not justify how their findings could be, either clinically or statistically, translated into DFR being a prognostic factor. The general rule, which was proposed by Hosmer and Lemeshow [5], only suggested poor-to-acceptable discrimination given the reported areas under the ROC in the original study. Conclusions that are based only on the values of areas under the ROC and lack appropriate justifications can again mislead others. Overestimating the prognostic role of DFR could lead to misinformed treatment plans and patient counselling, undermining both safety and effectiveness. Moreover, following the Bonferroni correction, any results with p-values ≥ 0.17 (based on the authors' approach) should have implied insignificance. This contradicts the authors' interpretation of the association between DFR and severity of CVT, which could be the authors' misunderstanding of multiplicity control. We suggest the authors to re-interpret their findings to avoid confusion. We also noticed an unusual trend in Fig. 3 of the paper where venous cerebral infarction was significantly associated with non-severe CVT [1]. While this is likely an error in data labelling or reference value, other potential causes cannot be ruled out, such as uncontrolled confounders/biases or overadjustment.

Abbreviations

CVT	Cerebral venous thrombosis
DFR	D-dimer to fibrinogen ratio
ROC	Receiver operating characteristic curve

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M-HT and K-HT-N reviewed the literature and this paper, drafted and revised the manuscript, read, and agreed to the final manuscript.

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Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

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