

Integrating clinical predictors and glial fibrillary acidic protein in prediction models for the prehospital identification of intracerebral haemorrhage in suspected stroke

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To cite: Almubayyidh M, Jenkins DA, Gaude E, *et al*. Integrating clinical predictors and glial fibrillary acidic protein in prediction models for the prehospital identification of intracerebral haemorrhage in suspected stroke. *BMJ Neurology Open* 2025;7:e001160. doi:10.1136/bmjno-2025-001160

► Additional supplemental material is published online only. To view, please visit the journal online (<https://doi.org/10.1136/bmjno-2025-001160>).

Received 24 April 2025
Accepted 02 June 2025



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ABSTRACT

Introduction Accurate and timely differentiation of intracerebral haemorrhage (ICH) from other suspected stroke cases is crucial in prehospital settings, where early blood pressure reduction in the ambulance can improve outcomes. This study aims to assess whether combining clinical predictors and glial fibrillary acidic protein (GFAP) in prediction models can effectively distinguish ICH from other suspected stroke cases.

Methods Data were derived from the Testing for Identification Markers of Stroke trial, a prospective diagnostic accuracy study. Suspected stroke patients within 6 hours of symptom onset were included. Clinical predictors were selected based on known associations with ICH, and a predefined GFAP cut-off of 290 pg/mL was applied. Logistic regression was used to assess the performance of clinical predictors and GFAP, individually and in combination. Internal validation and optimism correction were performed via bootstrapping, and comparisons of the area under the curve (AUC) were conducted using DeLong's test.

Results We included 209 suspected stroke cases, of which 5% were finally diagnosed with ICH. Clinical predictors alone achieved an optimism-corrected AUC of 0.74 (95% CI 0.60 to 0.88), while GFAP alone resulted in an optimism-corrected AUC of 0.83 (95% CI 0.69 to 0.99). Combining clinical predictors with GFAP significantly enhanced the AUC, yielding an optimism-corrected value of 0.90 (95% CI 0.79 to 0.98). This combined model also demonstrated high predictive accuracy, with an optimism-corrected sensitivity of 60% (95% CI 29.0% to 90.0%) and a specificity of 98% (95% CI 96.1% to 100.0%).

Conclusions Combining clinical predictors with GFAP shows promise for the prehospital identification of ICH to support transport decision-making and potentially initiate treatment while en route for these patients. Prospective validation using portable point-of-care devices is required to confirm the utility of this approach in the prehospital setting.

INTRODUCTION

Intracerebral haemorrhage (ICH) remains the most devastating form of stroke,

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Distinguishing patients with intracerebral haemorrhage (ICH) from other causes of suspected stroke in the prehospital setting is becoming increasingly important, as patients with ICH benefit from prehospital blood pressure lowering and rapid transfer to an appropriate stroke centre.

WHAT THIS STUDY ADDS

⇒ In this secondary analysis of a prospective observational study, we show that combining clinical predictors of ICH with glial fibrillary acidic protein (GFAP) could effectively distinguish patients with ICH from other suspected stroke cases with high predictive performance.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ If the findings of this study are validated using point-of-care GFAP testing devices, this combined approach could improve triage decisions and shorten the time to initiate ICH-specific interventions, particularly in the prehospital setting.

characterised by high mortality rates and poor functional outcomes.^{1 2} Early haematoma expansion is a major contributor to adverse outcomes, making its prevention the main therapeutic goal in the management of this challenging condition.^{3 4} Given the highly time-sensitive nature of treatment, there has been a growing emphasis on prehospital care to address the disease at its earliest stages.⁵ The INTERACT4 trial has demonstrated that prehospital blood pressure reduction reduces death and disability for patients later confirmed to have ICH, whereas this intervention was found to be harmful in patients with ischaemic stroke.⁶ Consequently, to facilitate future prehospital trials and ensure the safe, cost-effective implementation of such

interventions, there is a clear need for a simple, cost-effective, rapid and accurate diagnostic tool that can be employed by prehospital care providers to distinguish ICH from other diagnoses.

While there has been considerable interest in prehospital scales based on clinical features for this purpose,^{7–10} concerns persist regarding their real-world accuracy when used in isolation.¹¹ Recently, innovative technologies, such as brain-specific biomarker testing, have emerged as potentially easy-to-use and non-invasive strategies to support the early diagnosis and treatment of patients with different stroke subtypes in the prehospital setting.¹² Among these biomarkers, glial fibrillary acidic protein (GFAP)—an astrocyte marker that increases early following ICH—has shown diagnostic promise in differentiating patients with ICH.^{5 12} When combined with clinical predictors, GFAP's diagnostic accuracy could be further enhanced, which may facilitate more informed decision-making for patients with ICH in the field. Accordingly, the aim of this study is to investigate whether integrating clinical predictors of ICH and GFAP in prediction models can reliably identify ICH and differentiate it from other suspected stroke cases.

METHODS

This study was conducted in accordance with the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis checklist (online supplemental appendix 1).¹³

Data source and participant selection

Data were obtained from the TIME (Testing for Identification Markers of Stroke) trial,¹⁴ which enrolled consecutive patients with suspected stroke presenting via ambulance or directly to the emergency department within 18 hours of symptom onset in a prospective observational diagnostic accuracy study. The TIME trial received ethics approval from the WCG Western Institutional Review Board (Institutional Review Board tracking number: 20193270; study number: 1294597). Clinical data were collected, and all information was anonymised by the original study team, thus obviating the need for further ethical approval and patient consent for this study. For detailed information regarding the eligibility criteria, blood sampling and GFAP measurements, readers are referred to the original publication.¹⁴

Given that the benefits of treatment beyond 6 hours from symptom onset for patients with ICH remain unclear,¹¹ this investigation was limited to patients who presented within 6 hours of symptom onset. This subset reflects the cohort in which previous data support the diagnostic accuracy of GFAP,¹⁵ and it is also representative of patients typically seen in the prehospital setting.¹⁶

For this study, the outcomes were categorised into those with ICH and those with other diagnoses.

Selection of variables

To ensure consistency, the clinical predictors were selected for inclusion in the models based on our

previous findings,¹⁰ and their availability in the analysed dataset. Specifically, we considered male sex, unilateral arm weakness and systolic blood pressure levels, as these were found to be positively associated with ICH, alongside atrial fibrillation and coronary artery disease, which were associated with other diagnoses.¹⁰ Arm weakness in this study was derived from item 5 of the National Institutes of Health Stroke Scale, defined as a score of at least 1 point on either item 5a or 5b. For GFAP, we used a previously established cut-off value of 290 pg/mL.^{17 18}

Statistical analysis, model development and validation

Baseline characteristics were summarised as frequencies and percentages for categorical variables and as medians with IQRs for continuous data. Differences in plasma GFAP levels between ICH and other diagnoses were visualised using a boxplot, highlighting the median, IQR and any outliers. Group comparisons were performed using the Mann-Whitney U test, with statistical significance defined as $p < 0.05$. Notably, there were no missing data in the analysed dataset.

Logistic regression analyses were conducted to evaluate the ability of clinical predictors and GFAP, both individually and in combination, to differentiate ICH from other suspected stroke cases. To enhance the reliability of the findings, internal validation was performed using 1000 bootstrap resamples to adjust for optimism and obtain more realistic estimates. All performance metrics were reported with 95% CIs. The discriminatory performance of the models was assessed using the area under the curve (AUC), where a value of 0.5 indicates no discriminatory ability, meaning the model is no better than chance (flipping a coin) and 1.0 represents perfect discrimination, meaning that the model perfectly predicts the outcome.¹⁹ AUC comparisons between models were conducted using DeLong's test, with $p < 0.05$ indicating statistically significant differences.

Given the aim of this study, we further assessed the performance of the combined model (clinical predictors+GFAP). Specifically, we evaluated calibration using calibration curves, which compare actual and predicted probabilities. A perfectly calibrated model would align with a 45° line. Furthermore, the slopes and intercepts of the calibration curves were calculated, with a slope of 1 and an intercept of 0 representing ideal calibration. Additionally, a threshold probability cut-off of 0.3 was applied to this model to classify cases, aiming to optimise specificity while maintaining sensitivity. Finally, sensitivity and specificity were adjusted for optimism across the full range of threshold probabilities. All statistical analyses were conducted using R software (R Core Team, Vienna, Austria, V.4.2.2).

Patient and public involvement

No patients or members of the public were involved in the design of this study.

Table 1 Baseline characteristics of the investigated cohort

Variables	All patients (n=209)	ICH (n=10)	Other diagnoses (n=199)
Demographic			
Age (years), median (IQR)	64 (51–76)	66 (62–79)	63 (51–76)
Number of male patients, n (%)	82 (39)	2 (20)	80 (40)
Medical history, n (%)			
Hypertension	152 (73)	10 (100)	142 (71)
Diabetes mellitus	67 (32)	3 (30)	64 (32)
Atrial fibrillation	33 (16)	1 (10)	32 (16)
Coronary artery disease	37 (18)	1 (10)	36 (18)
Peripheral artery disease	2 (1)	0 (0)	2 (1)
Time intervals			
Onset time (min), median (IQR)	120 (69–204)	146 (93–239)	118 (69–203)
Symptoms, n (%)			
Facial droop	52 (25)	2 (20)	50 (25)
Arm weakness	58 (28)	6 (60)	52 (26)
Leg weakness	48 (23)	5 (50)	43 (22)
Speech impairment	82 (39)	7 (70)	75 (38)
Decreased level of consciousness	30 (14)	2 (20)	28 (14)
Vital signs			
SBP (mm Hg), median (IQR)	153 (136–171)	172 (143–199)	153 (136–170)
GFAP			
GFAP levels (pg/mL), median (IQR)	53 (13–101)	1663 (151–2706)	48 (13–95)

GFAP, glial fibrillary acidic protein; ICH, intracerebral haemorrhage; SBP, systolic blood pressure.

RESULTS

Clinical characteristics and GFAP levels

Of the 323 suspected stroke cases enrolled in the TIME trial,¹⁴ 209 were eligible for inclusion in this study. Among these, 10 patients (5%) were finally diagnosed with ICH, while 199 had other diagnoses, including 19 (9%) with large vessel occlusion (LVO) ischaemic stroke, 32 (15%) with non-LVO ischaemic stroke, 8 (4%) with transient ischaemic attack and 140 (67%) with stroke-mimicking conditions. The baseline characteristics of the investigated cohort are summarised in [table 1](#).

As illustrated in [figure 1](#), plasma GFAP levels differed significantly between the two groups, with higher levels observed in patients diagnosed with ICH compared with those with other conditions (1663 (151–2706) pg/mL vs 48 (13–95) pg/mL, $p<0.001$).

Performance and internal validation of the models

The apparent and optimism-corrected performance of clinical predictors and GFAP, both alone and in combination, is summarised in [figure 2](#). Overall, integrating clinical predictors with GFAP demonstrated superior performance in distinguishing ICH from other diagnoses compared with the use of clinical predictors or GFAP alone ([figure 2](#)).

The selected clinical predictors achieved an optimism-corrected AUC of 0.74 (95% CI 0.60 to 0.88), while GFAP alone demonstrated an optimism-corrected AUC of 0.83 (95% CI 0.69 to 0.99). The combination of clinical predictors with GFAP significantly enhanced the AUC compared with either the clinical predictors or GFAP alone ($p=0.038$ and $p=0.035$, respectively), yielding an optimism-corrected value of 0.90 (95% CI 0.79 to 0.98). This combined model achieved an optimism-corrected sensitivity of 60% (95% CI 29.0% to 90.0%) and a specificity of 98% (95% CI 96.1% to 100.0%), as shown in [table 2](#).

The corrected sensitivity and specificity of the combined model across different probability thresholds are presented in [figure 3](#). These thresholds can be adjusted to prioritise sensitivity or specificity, depending on clinical decision-making needs in patients with ICH. For instance, at a probability threshold of 0.67, the combined model achieves a sensitivity of 40% and a specificity of 100%.

The combined model also demonstrated slight miscalibration, with a tendency for overprediction at the lower end of the calibration curves ([figure 4](#)). The optimism-corrected slope and intercept were 1.12 (95% CI 1.06 to 1.19) and -0.07 (95% CI -0.10 to -0.04), respectively.

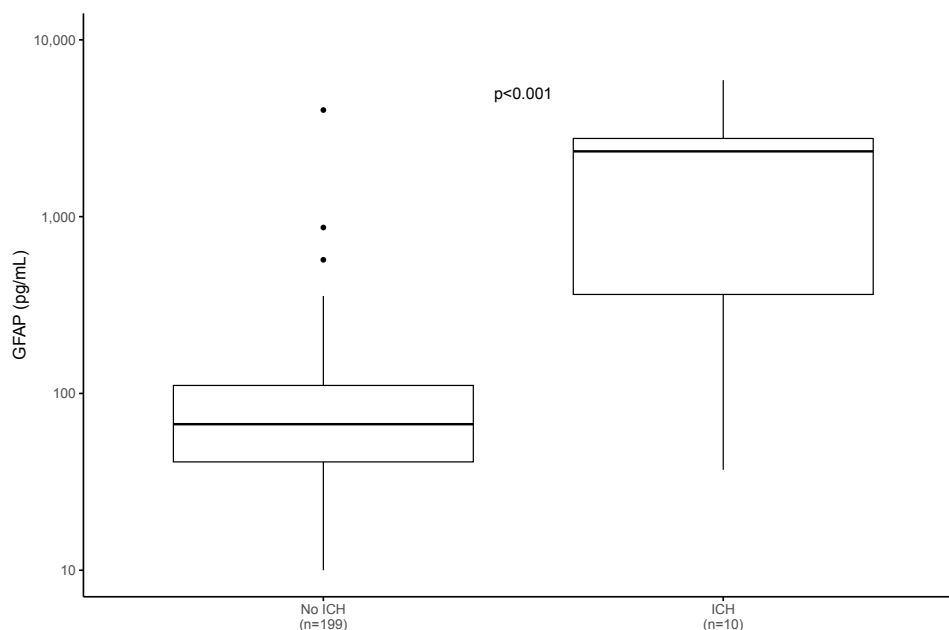


Figure 1 Boxplot of GFAP levels (pg/mL) comparing groups with and without ICH. GFAP, glial fibrillary acidic protein; ICH, intracerebral haemorrhage.

DISCUSSION

In patients presenting within 6 hours of stroke symptom onset, we demonstrated the potential to distinguish ICH from other suspected stroke cases by combining previously identified clinical predictors with GFAP measurements. These findings are

particularly valuable in light of recent advances in ICH management, such as those demonstrated in the INTERACT4 trial,⁶ and the development of portable point-of-care technologies capable of measuring GFAP levels within minutes.^{20–22} Such prediction methods could provide a cost-effective alternative to

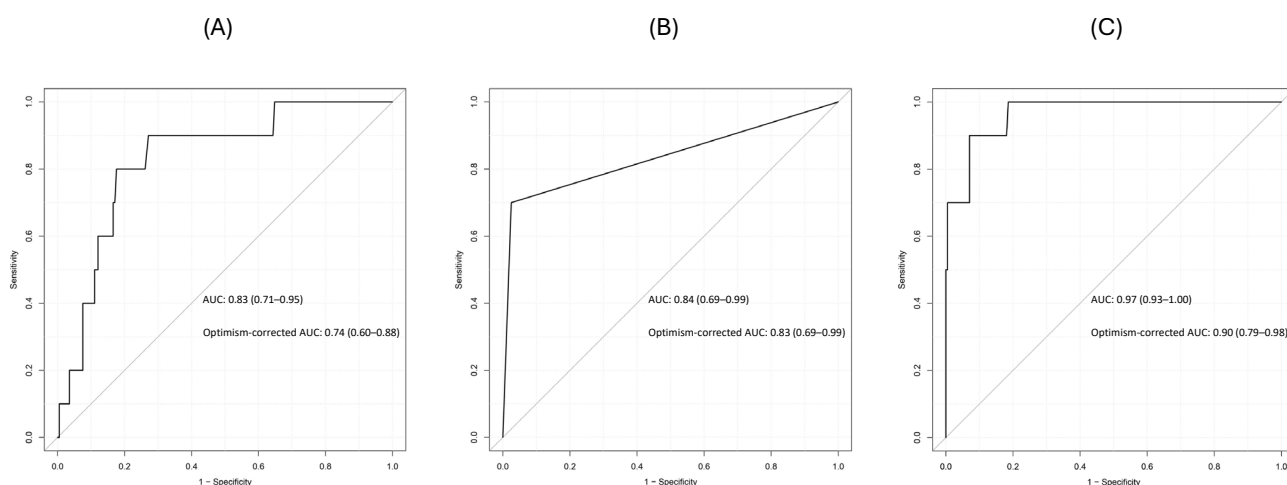


Figure 2 ROC curves for the models with apparent and optimism-corrected AUCs and their 95% CIs. (A) Clinical predictors, (B) GFAP, (C) clinical predictors+GFAP. AUCs, area under the curves; GFAP, glial fibrillary acidic protein; ROC, receiver operating characteristic.

Table 2 Performance of the combined model (clinical predictors+GFAP) for distinguishing patients with ICH

Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI)	Slope (95% CI)	Intercept (95% CI)
Apparent performance						
70% (34.8% to 93.3%)	99% (96.4% to 100.0%)	78% (44.4% to 97.5%)	99% (95.7% to 99.7%)	0.97 (0.93 to 1.00)	1.19 (1.12 to 1.26)	−0.11 (−0.14 to −0.08)
Optimism-corrected performance						
60% (29.0% to 90.0%)	98% (96.1% to 100.0%)	66% (37.8% to 94.4%)	98% (96.0% to 100.0%)	0.90 (0.79 to 0.98)	1.12 (1.06 to 1.19)	−0.07 (−0.10 to −0.04)

AUC, area under the curve; GFAP, glial fibrillary acidic protein; ICH, intracerebral haemorrhage; NPV, negative predictive value; PPV, positive predictive value.

mobile stroke units and could be used by prehospital personnel in ambulances to support decision-making for patients with ICH, leading to better transport decisions and earlier treatment strategies.

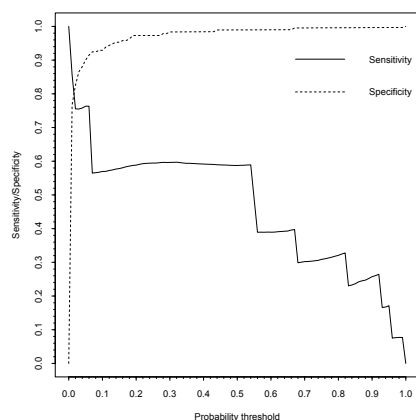
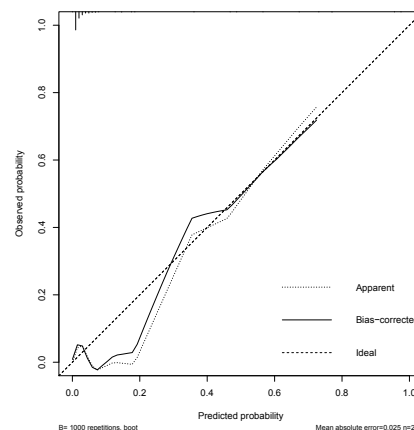
Consistent with previous research,^{17 23} we observed that plasma GFAP levels were significantly higher in cases of ICH than in other stroke subtypes and stroke mimics. This rapid increase in GFAP following ICH has been attributed to immediate astrocytic injury and the subsequent breakdown of the blood–brain barrier caused by the initial haematoma.⁵ In contrast, GFAP levels tend to rise more gradually in ischaemic stroke, as necrosis and cellular disintegration typically do not occur until 6–12 hours after symptom onset.²⁴ Meanwhile, in most stroke mimics, this protein remains undetectable in the bloodstream.²⁴

In this study, a predefined validated cut-off of 290 pg/mL was used for GFAP.^{17 18} However, multiple studies have shown a positive correlation between haematoma volume and GFAP levels,^{17 25} indicating that smaller ICH volumes (eg, <15 mL) may not result in an appreciable increase in GFAP.¹⁸ These findings suggest that achieving higher diagnostic sensitivity for distinguishing ICH from other suspected stroke cases may necessitate additional information,¹⁸ such

as the use of clinical predictors, as demonstrated in our study.

The combination of clinical predictors and GFAP achieved an AUC of 0.90, which was higher than the AUCs of either the clinical predictors or GFAP alone, as well as those reported in our previous prediction models.¹⁰ It should be noted that we used only five of the nine predictors previously identified,¹⁰ as these were the only ones available in the analysed dataset. Furthermore, the AUC of the combined model was also higher than the 0.71 reported by Jæger *et al*,²⁶ who examined a combination of a symptom-based stroke scale with GFAP for the identification of ICH in patients with suspected stroke.

At a probability threshold of 0.3, the combined model demonstrated a sensitivity of 60% and a specificity of 98%. This could assist prehospital personnel in determining whether to transport suspected ICH cases to the nearest acute stroke centre to avoid delays in necessary interventions, given the evidence that longer transport times can be detrimental to these patients.^{27 28} However, a specificity of 100% would still be required to ensure the safe treatment of ICH in suspected stroke cases and to avoid administering harmful therapies to patients with a different stroke subtype (eg, delivering intensive blood pressure-lowering or haemostatic interventions to those with ischaemic stroke). This 100% specificity was

**Figure 3** Corrected sensitivity and specificity at various probability thresholds for the combined model.**Figure 4** Calibration curves of the combined model.

achieved in the combined model at a probability cut-off of 0.67 (figure 3), although with a reduction in sensitivity to 40%. If early prehospital treatment is feasible for patients with ICH, direct transfer to a hospital with neurosurgical capabilities could be preferred to facilitate the prompt implementation of an ICH care bundle.²⁹

Several portable point-of-care devices have been developed to measure GFAP alongside other biomarkers, including the i-STAT Alinity, the LVOne test and the StrokeCheck device.^{20–22} The handheld i-STAT Alinity employs Abbott's i-STAT TBI (traumatic brain injury) plasma test cartridge to quantify GFAP and UCH-L1 (neuronal cell body biomarker ubiquitin C-terminal hydrolase-L1) from a single plasma sample.²⁰ The LVOne test consists of two portable lateral flow assays that use finger-prick capillary blood to measure D-dimer and GFAP.²¹ Similarly, the StrokeCheck device uses two lateral flow assays to measure GFAP and NT-proBNP (N-terminal pro-B-type natriuretic peptide).²² By integrating GFAP measurements from these devices with distinguishing predictors of ICH, prehospital personnel could make more informed transport decisions on scene and potentially initiate treatment for ICH cases while en route to the hospital, thereby improving patient outcomes. However, this promising approach has yet to be evaluated in a large prehospital trial involving unselected patients with suspected stroke.

Limitations

This study is subject to inherent limitations, and the results should therefore be interpreted with caution. Specifically, our findings are constrained by the small sample size, which falls below the minimum required for the number of predictors considered, based on the sample size criteria proposed by Riley *et al.*³⁰ This limitation could potentially lead to overfitting and limit the generalisability of our results. Moreover, our findings were not externally validated; however, bootstrap validation was employed to address optimism, which is generally considered superior to data splitting.³⁰ Furthermore, the prevalence of ICH in the dataset was approximately 5%, lower than the 10% assumed in suspected stroke cases.³¹ It is important to note that prevalence can vary between countries and should be accounted for in future research. Finally, GFAP measurements in the TIME trial were performed using laboratory immunoassays, and other common predictors of ICH, such as headache, vomiting and neurological deterioration, were not collected.¹⁴

These limitations highlight the need for a properly designed and well-powered prospective validation study using point-of-care devices in combination with the investigated predictors and other common predictors to confirm our findings and ensure reliable application in prehospital settings.

CONCLUSIONS

Integrating clinical predictors and GFAP into a predictive model represents a promising approach for distinguishing patients with ICH from other suspected stroke cases in the prehospital setting. This combined method has the potential to enhance triage to the appropriate level of care and reduce the time between symptom onset and the initiation of ICH-specific interventions, particularly in the prehospital setting, thereby improving outcomes. However, prospective validation of this combined approach, using point-of-care devices to measure GFAP levels, is necessary to confirm our findings.

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Contributors All authors of this study meet the criteria for authorship. MA is the primary author and guarantor of this study under the supervision of ARP-J and DAJ. MA conceptualised the study and designed the methods, integrating feedback from ARP-J, DAJ and EG. MA had full access to all data and accepts responsibility for the integrity and accuracy of the analysis. MA prepared the initial manuscript draft with support from ARP-J, DAJ and EG. All authors critically reviewed the manuscript and approved the final version for submission.

Funding The study is part of MA's PhD project, which is funded by King Saud University, Riyadh, Saudi Arabia (grant no: NA), through the Saudi Arabian Cultural Bureau in the United Kingdom (grant no: NA). The funders had no involvement in the study design, data analysis, manuscript writing or the decision to submit the work for publication.

Competing interests EG is a shareholder of Pockit Diagnostics Ltd, which manufactures the LVOne test. The rest of the authors have no competing interest.

Patient consent for publication Not applicable.

Ethics approval No additional approval was necessary because an anonymised dataset was used for this secondary analysis.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. The data analysed in this study were obtained from the TIME trial. Requests to access the database should be directed to edoardo.gaude@pockitdx.co.uk. All R code used in this study is available upon request from the corresponding author.

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