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ORIGINAL RESEARCH

Predicting White Matter Hyperintensity: Leveraging Portable Magnetic Resonance Imaging for Accessible Brain Health Screening

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ABSTRACT

BACKGROUND AND PURPOSE: Portable MRI (pMRI) has emerged as a cost-effective and accessible tool for the identification of white matter hyperintensities (WMH), an independent risk factor for stroke and dementia. Our objective was to confirm that pMRI can produce accurate WMH measurements and to develop and validate a risk model to predict WMH on pMRI for the purpose of identifying patients who may benefit from pMRI screening.

MATERIALS AND METHODS: The development (N=143) and validation (N=127) cohorts included patients without acute neurologic pathology who received a pMRI at a tertiary care hospital between May 2020 and July 2024. The development cohort included pMRIs collected as part of a prospective WMH screening pilot program in the emergency department. The validation cohort was a retrospective collection of pMRIs obtained for separate research purposes. Conventional MRIs (cMRIs) in the validation cohort obtained within 3 months of pMRIs were used for additional validation and device agreement. The primary outcome was WMH burden greater than 10 mL, assessed via an axial T2-FLAIR sequence acquired on a 0.064 T pMRI and quantified using a WMH segmentation software developed to process sequences of any resolution. We used backwards selection to screen candidate variables and report the area under the curve of the resulting model.

RESULTS: The final model, which included age, systolic blood pressure >140, atrial fibrillation, and tobacco use, achieved an AUC of 0.83 (95% CI 0.75-0.90) in the development cohort (N=143, 62.4±12.6 years, 44% female, 36% non-white race) and 0.85 (95% CI 0.77-0.92) in the validation cohort (N=127, 65.2±16.8 years, 51% female, 34% non-white race), with similar results using WMH measurements derived from cMRI (N=120, p=0.98, AUC=0.86, 95% CI 0.77-0.93). Additionally, we confirmed agreement in WMH volumes between pMRI and cMRI (N=120, r=0.93, 95% CI 0.90-0.95, p<0.001).

CONCLUSIONS: The WMH risk score demonstrated accurate performance and reproducibility across cohorts, supporting its potential as a screening tool for identifying patients at risk of significant WMH burden. Appropriately targeted pMRI screening in high-risk individuals could allow providers and patients to proactively manage vascular risk factors and improve neurological outcomes.

ABBREVIATIONS: pMRI = portable magnetic resonance imaging; cMRI = conventional magnetic resonance imaging; WMH = white matter hyperintensity; hypertension = HTN; diabetes = DM; atrial fibrillation = AFib; systolic blood pressure = SBP; hyperlipidemia = HLD; area under the curve = AUC; receiver operating characteristic = ROC.

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SUMMARY SECTION

PREVIOUS LITERATURE: White matter hyperintensities (WMH) are an established biomarker of vascular brain health, associated with stroke and dementia. While conventional MRI is the standard for WMH detection, its high cost and limited accessibility have prevented widespread screening. Portable MRI (pMRI) has emerged as an alternative, providing accurate WMH measurements at a fraction of the cost. Future efforts deploying pMRI for brain health screening would benefit from objective tools to triage patients by risk for clinically actionable WMH burden. We have addressed this need by developing and validating a WMH prediction model tailored for pMRI.

KEY FINDINGS: We developed a WMH risk model using pMRI data, incorporating age, systolic blood pressure >140, atrial fibrillation, and tobacco use, demonstrating high accuracy in the development (AUC=0.83) and validation (AUC=0.85) cohorts. Additionally, we confirmed strong correlation between pMRI and conventional MRI WMH measurements (r=0.93).

KNOWLEDGE ADVANCEMENT: This study presents a WMH risk model that may be used to identify patients with the greatest risk for severe WMH burden. Identifying high risk patients may allow providers to fairly and efficiently deploy pMRI resources where they will have the greatest impact.

INTRODUCTION

As the global population ages, the economic and health burden caused by dementia and cerebrovascular injury emphasizes the need for biomarkers to detect changes in brain health before the onset of neurodegenerative disease and brain injury. White matter hyperintensities (WMH) are one such biomarker that are well-established indicators of vascular brain health and are an independent risk factor for cardiovascular disease, stroke, and dementia.[1–5] WMH are most often attributed to cerebral small vessel disease and are strongly linked to vascular risk factors, including hypertension (HTN), diabetes (DM), atrial fibrillation (AFib), and tobacco use.[6–13] Management of risk factors can slow WMH accumulation, making early detection a promising opportunity to proactively support brain health.[14] However, large-scale WMH screening remains constrained by the high cost and accessibility barriers of conventional MRI, particularly for socioeconomically disadvantaged populations.

Portable MRI (pMRI) has emerged as a cost-effective and accessible tool for the identification of WMH. pMRI devices are available at a fraction of the cost of conventional MRI units, are compact enough to be brought directly to patients, and can be deployed anywhere with a standard 120V wall outlet. Additionally, their low-field magnet does not present the same risk as conventional MRI, and they can be operated without the need for dedicated technicians or shielding. Recent studies have assessed the image quality and accuracy of pMRI in hospital and outpatient cohorts with neurologic disease, including WMH, with high reliability.[15–23] Leveraging pMRI for WMH detection could enable large-scale screening efforts previously unattainable due to resource constraints.

Previously developed WMH risk models have found age and HTN to be the strongest predictors of WMH.[24,25] To confirm these findings, and to develop a model that is uniquely suited to facilitate patient triage for pMRI screening, we have developed and validated a WMH risk prediction model built specifically with pMRI data that incorporates readily available clinical and demographic variables. We hypothesized that this risk score would accurately predict clinically actionable WMH burden, allowing providers to prioritize the delivery of pMRI resources to patients with the highest risk for WMH. Additionally, we sought to provide further confirmation that pMRI can provide accurate WMH measurements in a large and diverse cohort.

We believe that a WMH risk score would enable unbiased and efficient delivery of pMRI screening to patients facing the greatest need for imaging. Disparities in access to diagnostic imaging disproportionately affect racial minorities and economically disadvantaged patients, populations at higher risk of cardiovascular disease and dementia.[26–33] The emergency department, as a safety-net setting, often serves as the primary point of care for high risk individuals.[34] Thus, this environment provides a unique opportunity to identify patients who are both at high risk for the neurological consequences of inadequate vascular risk factor control and face the greatest barriers to accessible neuroimaging.

MATERIALS AND METHODS

Development and Validation Cohorts

The development cohort was made up of 143 patients who participated in a pilot program for WMH screening among patients with at least one vascular risk factor. Patients were prospectively enrolled at a tertiary care emergency department between December 2021 and July 2024. Participants were approached for the study based on the presence of cardiovascular risk factors, including systolic blood pressure (SBP) above 160 upon presentation, medical history of HTN, use of anti-hypertensive medications, HLD, DM, AFib, or other cardiovascular disease. All 143 participants underwent a pMRI study on a 0.064 T MRI (Swoop (Version 8.1-9.0), Hyperfine Inc., Guilford, CT) with 124 completing a Montreal Cognitive Assessment. The pMRI study included an axial T2-FLAIR following manufacturer's

standard protocol (repetition time msec/echo time msec/inversion time (TR/TE/TI) = 4000/234/1400 msec; in-plane resolution = 1.6 x 1.6 mm; slice thickness = 5 mm; study time = 9:35 min). Each pMRI study was reviewed for significant artifacts. Based on this review, we did not exclude any scans from the analysis. Candidate risk variables for model construction were collected by bedside questionnaire. Patients with incomplete questionnaires were backfilled using data from the EHR. Inclusion criteria for the analysis were absence of acute neurological pathology and a completed pMRI scan. Given our goal to estimate risk of WMH before the development of stroke or other cerebrovascular pathology, we excluded 16 patients with a prior stroke. Six patients with incomplete questionnaires were completed using data from the EHR.

Table 1. Clinical characteristics in development and validation cohort.

Characteristic	Development cohort (n=143)	Validation cohort (n=127)	*P* value
Age	62.4±12.6	65.2±16.8	0.12
Female Sex	63 (44%)	65 (51%)	0.24
BMI	31.4±17.2	-	
Non-white race	51 (36%)	43 (34%)	0.80
Hispanic	21 (15%)	-	
≥ College education	57 (42%)	-	
Employment status			
Employed	64 (47%)	-	
Unemployed	21 (16%)	-	
Retired	50 (37%)	-	
Insured	128 (93%)	-	
Usual source of care			
Community health center	9 (6%)	-	
Hospital clinic or outpatient department	31 (23%)	-	
Private doctor's office	92 (68%)	-	
Hypertension	100 (72%)	92 (72%)	0.93
Systolic blood pressure > 140	77 (54%)	66 (52%)	0.76
Antihypertensive medication	93 (65%)	77 (61%)	0.46
Congestive heart failure	15 (11%)	-	
Myocardial Infarction	21 (13%)	-	
Repeated falls	53 (39%)	-	
Atrial fibrillation	22 (16%)	30 (24%)	0.13
Hyperlipidemia	98 (71%)	80 (63%)	0.17
Diabetes	45 (33%)	48 (38%)	0.38
Current smoker	17 (13%)	14 (11%)	0.57
Alcohol use	43 (32%)	42 (33%)	0.80
Montreal Cognitive Assessment (n=124)	24 (21-26 IQR)	-	
WMH Volume (mL)	9.2±6.4	11.9±8.4	0.02

Binary variables presented as n (%); ordinal variables as median (interquartile range); and continuous variables as mean±SD. T-test for continuous variables and Chi-Squared tests for categorical variables were used to compare the development and validation cohort across demographic and clinical variables. Given the non-parametric distribution of WMH burden in both cohorts, a Mann-Whitney U test was used to compare WMH burden. Of note, the validation cohort is a limited data set that does not include variables that were part of the demographic survey given to patients in the development cohort, resulting in fewer variables available in the validation cohort.

The validation cohort included a limited data set of 127 pMRIs obtained retrospectively at the same hospital for separate research projects utilizing pMRI between May 2020 and July 2024. We included all patients who received a physician-requested or research portable MRI, did not have acute intracranial pathology, and consented to retrospective analysis of their imaging studies and health records. We excluded two patients who declined health record access. In this cohort, 120 patient cMRIs with axial T2-FLAIR obtained within 3 months of pMRI were included for additional validation of pMRI WMH measurements and model performance on conventional images. cMRI studies were obtained on a 3 T device using an 8-channel sensitivity encoding head coil (MAGNETOM Verio, Siemens, Erlangen, Germany) with the following protocol for axial T2-FLAIR: repetition time msec/echo time msec/inversion time (TR/TE/TI) = 9000/91/2500 msec; in-plane resolution = 1.6 x 1.6 mm; slice thickness = 5.0 mm; study time = 5:30 min. This study operated under a research protocol approved by the university Institutional Review Board and informed consent was obtained from all participants.

WMH Measurement and Volume Agreement

The primary outcome was moderate to severe WMH. To assess WMH burden, axial T2-FLAIR acquisitions were processed using WMH-SynthSeg in FreeSurfer, a validated open-source machine learning algorithm built to measure WMH on MRI sequences of any contrast or

resolution, including pMRI.[22] We excluded patients with acute brain injury as any hyperintense pathology can be erroneously flagged as WMH by WMH-SynthSeg. We defined moderate to severe WMH burden as a volume greater than or equal to 10 mL, previously established as the threshold for clinically relevant WMH.[35–37] To assess volumetric agreement between devices, patients in the validation cohort with cMRI obtained within three months of patient pMRIs were also processed with WMH-SynthSeg. We compare raw cMRI and pMRI volumes and assess device agreement in detection of moderate to severe WMH (>10 mL).

Variable Selection and Model Construction

Candidate WMH risk variables included previously established risk factors and variables that are readily available in the EHR. In the development cohort, we collected 20 clinical and demographic variables from each patient (Table 1). A backwards stepwise logistic regression model (p=0.1) was used to identify the strongest predictors of WMH in the development cohort. Accuracy of the model was measured by the area under the curve (AUC) of the receiver operating curve (ROC). With a clinical interest in maximizing sensitivity while maintaining a specificity greater than 40%, we used a positive outcome threshold of >0.2 to select a ROC cut-point. The model was then applied to the validation cohort using volumes from both pMRI and cMRI with DeLong's test used to compare ROC curves. The TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis) + AI checklist was followed in adherence with standardized reporting of prediction models (see Online Supplemental Data).

Statistical Analysis

All statistical analysis was performed in Python (Version 3.13.1, Python Software Foundation). Pearson's correlation and Cohen's kappa (κ) were used to assess pMRI and cMRI agreement in raw volumes and detection of WMH over 10 mL respectively. T-test for continuous variables and Chi-Squared tests for categorical variables were used to compare the development and validation cohort across demographic and clinical variables. Given the non-parametric distribution of WMH burden in both cohorts, a Mann-Whitney U test was used to compare WMH burden. A p-value < 0.05 was considered statistically significant. Study data is available upon request.

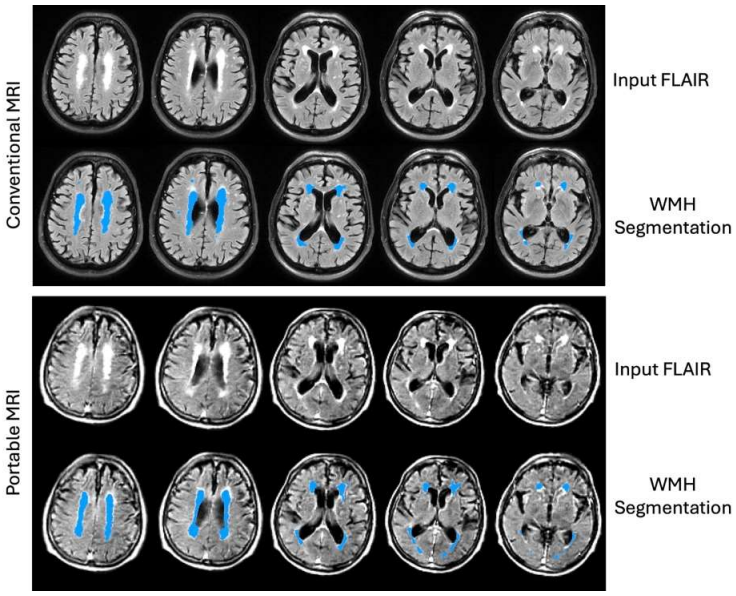

FIG 1. Representative example of WMH detection on pMRI, with paired cMRI and automatically segmented lesions outlined (blue).

RESULTS

Development Cohort

The WMH prediction model was trained on data from 143 participants (mean 62.4±12.6 years, 44% female, 36% non-white race) who presented to an urban tertiary care emergency department between December 2021 and July 2024. A complete summary of clinical and demographic characteristics is available in Table 1. 72% of patients had a diagnosis of HTN, 65% were taking an anti-hypertensive medication, 54% had a SBP over 140, 16% had AFib, 71% had HLD, 33% had DM, 32% reported alcohol use, and 13% reported tobacco use. The median (IQR) WMH burden was 7.5 (5.1-11.1) mL, with 29% of participants presenting with moderate to severe WMH. An example of the pMRI axial FLAIR acquisition with a paired cMRI and automated WMH segmentation is shown in Fig 1. Through backwards selection, we identified four variables to be included in the final WMH prediction model: age, diagnosis of AFib, tobacco use, and SBP > 140 (Table 2). The AUC for the risk model in the development cohort was 0.83 (95% CI 0.75-0.90); for a positive outcome threshold >0.2, the model was 86% sensitive and 61% specific (Fig 2A).

Validation Cohort

The validation cohort included 127 patients (65.2±16.8 years, 51% female, 34% non-white race) enrolled between May 2020 and July 2024. Vascular risk factors were present at similar rates to the development cohort: 72% of patients had a diagnosis of HTN, 61% were taking a BP medication, 52% had a systolic BP over 140, 24% had AFib, 63% had HLD, 38% had DM, 33% reported alcohol use, and

11% were current smokers (Table 1). Demographic and clinical variables did not differ significantly between cohorts (all p > 0.05, Table 1). The median (IQR) WMH burden in this cohort was 9.2 (5.2-16.7) mL, with 46% of participants presenting with greater than 10 mL WMH. The WMH burden in the validation cohort was significantly higher than the development cohort (p=0.02). The AUC in the validation cohort was 0.85 (95% CI 0.77-0.92); for a positive outcome threshold of >0.2 the model was 97% sensitive and 60% specific (Fig 2B). In this cohort, both age (p<0.001) and systolic BP over 140 (p=0.002) were significantly associated with WMH over 10 mL, while Afib (p=0.17) and tobacco use (p=0.82) were not. Finally, applying the model to WMH volumes derived from 120 cMRI studies in the validation cohort produced nearly identical results (p=0.98, AUC=0.86 95% CI 0.77-0.93).

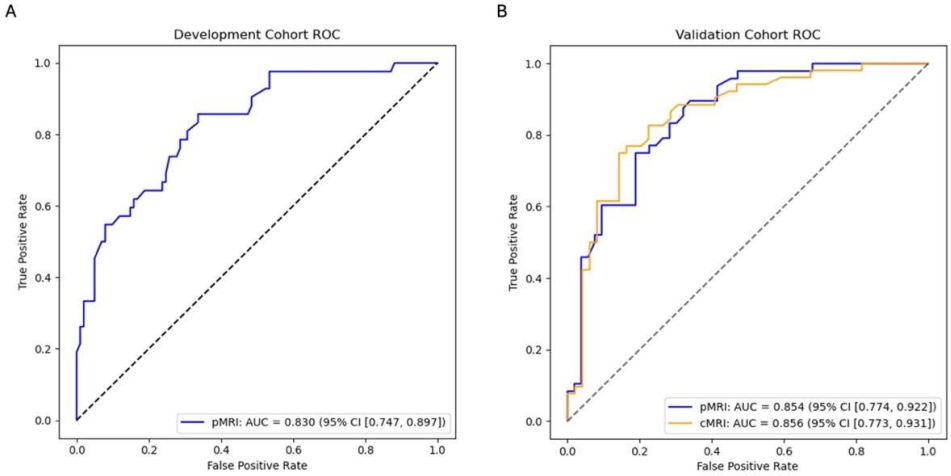

FIG 2. ROC curves for the WMH prediction model applied to the (A) development (N=147) and (B) validation (N=127) cohorts. AUC in the development cohort was 0.830 (95% CI 0.747-0.897) and 0.854 (95% CI 0.774-0.922) in the validation cohort using pMRI WMH volumes as the outcome variable. When using cMRI WMH volumes in the validation cohort (N=120), the AUC was 0.856 (95% CI 0.773-0.931).

Table 2. Multivariable logistic regression model predicting WMH.

Variable	Coefficient	Multivariate analysis OR (95% CI)	P value
Age	0.110	1.12 (1.07-1.17)	<0.001
Atrial Fibrillation	1.539	4.66 (1.44-15.05)	0.01
Tobacco Use	1.704	5.497 (1.45-20.77)	0.01
Systolic BP>140	1.115	3.05 (1.19-7.81)	0.02

Agreement in pMRI vs cMRI

Among all paired pMRI and cMRI in the validation cohort, WMH volumes showed strong correlation (N=120, r=0.93, 95% CI 0.90-0.95, p<0.001) (Fig 3). Additionally, there was strong agreement between devices for detection of moderate to severe WMH (>10 mL) (κ=0.83), confirming the reliability of pMRI to assess WMH burden. On average, pMRI underestimated WMH burden by 6.3%. There were no significant outliers when comparing volumes between devices (Z-score >3).

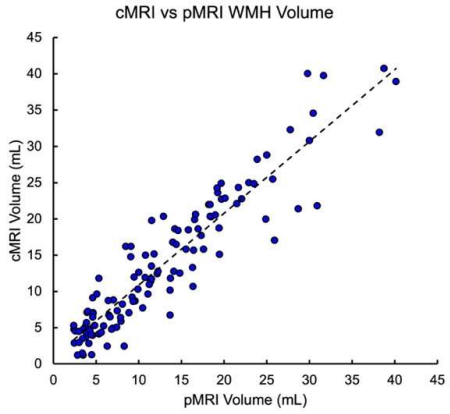

FIG 3. WMH volume scatterplot and linear fit of WMH volumes from pMRI compared to cMRI using WMH-SynthSeg ($r = 0.93$ (95% CI 0.90-0.95), $p < 0.001$).

DISCUSSION

This study presents a patient-level risk model for predicting clinically actionable WMH burden. The model leverages four readily available clinical factors: age, diagnosis of atrial fibrillation, tobacco use, and systolic BP over 140, all of which are well-established WMH risk factors. [6,8,9,13,14] The present model mirrors others in its consideration of HTN and age as significant predictors of WMH, while including Afib and tobacco use as additional variables to consider.[24,25] Our model was validated across two independent cohorts, supporting its utility in clinical and research settings. The high sensitivity of this model, along with the strong agreement in WMH volumes between pMRI and cMRI, demonstrates the potential of pMRI as a transformative tool for brain health monitoring.[20,23] We believe that this model could be used to help clinicians fairly and efficiently provide portable MRI scans to patients with the highest risk for clinically actionable WMH. While practice guidelines currently do not recommend clinical interventions for WMH, making brain MRI accessible to ascertain WMH may further future investigation.

While the prohibitive cost of large-scale WMH screening has made individual risk scores unnecessary, recent developments in pMRI technology have opened the door to cost-effective and accessible screening. Through robust agreement of pMRI and cMRI WMH volumes ($r=0.93$), and ability of pMRI to detect moderate to severe WMH ($\kappa=0.83$), we have confirmed that pMRI is a reliable and accurate tool for WMH ascertainment. These measures together indicate that while there may be small differences in WMH volume between pMRI and cMRI, these differences would not change clinical interpretations of WMH burden. While the lower magnetic field strength of pMRI reduces the signal-to-noise ratio and thus reduces image resolution, advancements in machine learning tools like WMH-SynthSeg and on-device AI image reconstruction have shown that low-field devices can nonetheless produce images of sufficient quality.

Given that up to 90% of stroke risk and 50% of dementia risk is modifiable, it is imperative that our healthcare networks develop infrastructure to proactively monitor brain health.[42–44] While several factors contribute to brain health, WMH stands out as a prominent biomarker due to its close association with vascular health, stroke, and dementia.[1-5] Measuring WMH as a surrogate for brain health will allow physicians to assess risk for multiple cerebrovascular pathologies and will provide patients with a salient marker of the impact that vascular risk factors have on their brain. pMRI technology enables early detection of WMH on a scale far beyond what was previously feasible. As pMRI is deployed in new settings, WMH risk stratification will be necessary to fairly allocate resources to those with the highest risk of clinically actionable WMH, while avoiding unnecessary burden to primary care and safety-net services. Additionally, risk stratification may be applied to clinical trials assessing the feasibility of large-scale WMH screening.

A major strength of the present model is the diversity of the development cohort. This cohort closely mirrors the general population across race, sex, and education level. Additionally, the emergency department is often where disadvantaged populations with unmanaged vascular risk factors access the healthcare system, making it a setting where many would benefit from WMH screening. The median WMH volume in the development cohort (7.5 mL) is comparable to another population-based cohort of similar average age (6.8 mL), indicating that this model may predict WMH burden in the general population.[45] Additionally, the model's accurate performance in both cohorts despite the significant difference in WMH burden ($p=0.02$) demonstrate that it may be generalizable to populations with variable WMH burden; however, further use of pMRI in the general population is necessary to validate this claim. The model is further strengthened by the fact that it was developed using pMRI data, making it uniquely equipped for immediate use with this imaging modality. At the same time, its accurate performance using standard-of-care images indicates that it can also be applied to screening efforts utilizing conventional MRI. While we believe that this model can accurately predict WMH burden, an MRI, either portable or conventional, is ultimately necessary to make a definitive determination of WMH severity.

This model has several potential limitations. First, the development cohort was smaller than other population-based cohorts that have assessed WMH. Additionally, this cohort was comprised of patients with at least one vascular risk factor who presented to the ED, potentially biasing the model towards higher WMH burden and limiting its generalizability to the general population or younger populations. Furthermore, the validation cohort, selected from patients with a wide range of clinical presentations, including suspected strokes, complaints of dizziness, post pituitary resections, and COVID, is unlikely to represent a random sample of the population, limiting its generalizability. The present model prioritizes high sensitivity (86-97%) meaning that very few patients with high WMH will be incorrectly categorized as low risk; on the other hand, the model may generate up to 40% false positives. While pMRI presents minimal patient risk, we recognize that the high false positive rate may lead to the use of pMRI in cases where it is not needed.

We must also consider the potential limitations of pMRI technology. While we have demonstrated robust agreement between pMRI and cMRI, the lower resolution of pMRI may prevent the accurate detection of smaller WMH volumes. Additionally, while the pMRI exam can be completed in 15 minutes by clinical staff with limited training, this analysis does not address workflow in the primary care or outpatient setting.

These limitations need to be explored with continued research in population-based cohorts and a focus on the potential costs and benefits of screening initiatives. Future research applying this model to WMH screening in a primary care setting, especially with longitudinal health outcomes, will further support its clinical utility.

CONCLUSIONS

This study presents a validated risk model for predicting WMH burden. Four simple clinical factors, age, systolic blood pressure > 140 mm Hg, atrial fibrillation, and tobacco use, predicted WMH burden in pMRI with high sensitivity and robust performance across cohorts, supporting its utility for targeted screening in diverse populations. The integration of this risk model with pMRI offers a practical tool to identify patients who should receive a pMRI for WMH detection, particularly in underserved settings where conventional imaging access is limited. Early WMH detection in high-risk patients will enable proactive risk factor management, with the potential to improve outcomes in brain and cardiovascular health. Future investigation applying this model as a screening tool in primary care or emergency department cohorts should be explored.

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TRIPOD+AI

Version: 11-January-2024

Section/Topic	Item	Development / evaluation[1]	Checklist item	Reported on page
TITLE				
Title	1	D;E	Identify the study as developing or evaluating the performance of a multivariable prediction model, the target population, and the outcome to be predicted	1
ABSTRACT				
Abstract	2	D;E	See TRIPOD+AI for Abstracts checklist	1
INTRODUCTION				
Background	3a	D;E	Explain the healthcare context (including whether diagnostic or prognostic) and rationale for developing or evaluating the prediction model, including references to existing models	1, 2
	3b	D;E	Describe the target population and the intended purpose of the prediction model in the context of the care pathway, including its intended users (e.g., healthcare professionals, patients, public)	2
	3c	D;E	Describe any known health inequalities between sociodemographic groups	2
Objectives	4	D;E	Specify the study objectives, including whether the study describes the development or validation of a prediction model (or both)	2
METHODS				
Data	5a	D;E	Describe the sources of data separately for the development and evaluation datasets (e.g., randomised trial, cohort, routine care or registry data), the rationale for using these data, and representativeness of the data	2, 3
	5b	D;E	Specify the dates of the collected participant data, including start and end of participant accrual; and, if applicable, end of follow-up	2, 3
Participants	6a	D;E	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including the number and location of centres	2, 3
	6b	D;E	Describe the eligibility criteria for study participants	3
	6c	D;E	Give details of any treatments received, and how they were handled during model development or evaluation, if relevant	3
Data preparation	7	D;E	Describe any data pre-processing and quality checking, including whether this was similar across relevant sociodemographic groups	4
Outcome	8a	D;E	Clearly define the outcome that is being predicted and the time horizon, including how and when assessed, the rationale for choosing this outcome, and whether the method of outcome assessment is consistent across sociodemographic groups	3
	8b	D;E	If outcome assessment requires subjective interpretation, describe the qualifications and demographic characteristics of the outcome assessors	N/A
	8c	D;E	Report any actions to blind assessment of the outcome to be predicted	N/A
Predictors	9a	D	Describe the choice of initial predictors (e.g., literature, previous models, all available predictors) and any pre-selection of predictors before model building	6
	9b	D;E	Clearly define all predictors, including how and when they were measured (and any actions to blind assessment of predictors for the outcome and other predictors)	3, 4
	9c	D;E	If predictor measurement requires subjective interpretation, describe the qualifications and demographic characteristics of the predictor assessors	3, 4
Sample size	10	D;E	Explain how the study size was arrived at (separately for development and evaluation), and justify that the study size was sufficient to answer the research question. Include details of any sample size calculation	2, 3
Missing data	11	D;E	Describe how missing data were handled. Provide reasons for omitting any data	3
Analytical methods	12a	D	Describe how the data were used (e.g., for development and evaluation of model performance) in the analysis, including whether the data were partitioned, considering any sample size requirements	4
	12b	D	Depending on the type of model, describe how predictors were handled in the analyses (functional form, rescaling, transformation, or any standardisation).	N/A
	12c	D	Specify the type of model, rationale[2], all model-building steps, including any hyperparameter tuning, and method for internal validation	4
	12d	D;E	Describe if and how any heterogeneity in estimates of model parameter values and model performance was handled and quantified across clusters (e.g., hospitals, countries). See TRIPOD-Cluster for additional considerations[3]	4
	12e	D;E	Specify all measures and plots used (and their rationale) to evaluate model performance (e.g., discrimination, calibration, clinical utility) and, if relevant, to compare multiple models	4
	12f	E	Describe any model updating (e.g., recalibration) arising from the model evaluation, either overall or for particular sociodemographic groups or settings	N/A
	12g	E	For model evaluation, describe how the model predictions were calculated (e.g., formula, code, object, application programming interface)	4
Class imbalance	13	D;E	If class imbalance methods were used, state why and how this was done, and any subsequent methods to recalibrate the model or the model predictions	N/A
Fairness	14	D;E	Describe any approaches that were used to address model fairness and their rationale	N/A
Model output	15	D	Specify the output of the prediction model (e.g., probabilities, classification). Provide details and rationale for any classification and how the thresholds were identified	5

[1] D=items relevant only to the development of a prediction model; E=items relating solely to the evaluation of a prediction model; D;E=items applicable to both the development and evaluation of a prediction model

[2] Separately for all model building approaches.

[3] TRIPOD-Cluster is a checklist of reporting recommendations for studies developing or validating models that explicitly account for clustering or explore heterogeneity in model performance (eg, at different hospitals or centres). Debray et al, BMJ 2023; 380: e071018 [DOI: 10.1136/bmj-2022-071018]

Training versus evaluation	16	D;E	Identify any differences between the development and evaluation data in healthcare setting, eligibility criteria, outcome, and predictors	5
Ethical approval	17	D;E	Name the institutional research board or ethics committee that approved the study and describe the participant-informed consent or the ethics committee waiver of informed consent	3
OPEN SCIENCE				
Funding	18a	D;E	Give the source of funding and the role of the funders for the present study	7
Conflicts of interest	18b	D;E	Declare any conflicts of interest and financial disclosures for all authors	1
Protocol	18c	D;E	Indicate where the study protocol can be accessed or state that a protocol was not prepared	3
Registration	18d	D;E	Provide registration information for the study, including register name and registration number, or state that the study was not registered	3
Data sharing	18e	D;E	Provide details of the availability of the study data	3
Code sharing	18f	D;E	Provide details of the availability of the analytical code[4]	N/A
PATIENT & PUBLIC INVOLVEMENT				
Patient & Public Involvement	19	D;E	Provide details of any patient and public involvement during the design, conduct, reporting, interpretation, or dissemination of the study or state no involvement.	2, 3
RESULTS				
Participants	20a	D;E	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	4
	20b	D;E	Report the characteristics overall and, where applicable, for each data source or setting, including the key dates, key predictors (including demographics), treatments received, sample size, number of outcome events, follow-up time, and amount of missing data. A table may be helpful. Report any differences across key demographic groups.	4
	20c	E	For model evaluation, show a comparison with the development data of the distribution of important predictors (demographics, predictors, and outcome).	4
Model development	21	D;E	Specify the number of participants and outcome events in each analysis (e.g., for model development, hyperparameter tuning, model evaluation)	4
Model specification	22	D	Provide details of the full prediction model (e.g., formula, code, object, application programming interface) to allow predictions in new individuals and to enable third-party evaluation and implementation, including any restrictions to access or re-use (e.g., freely available, proprietary)[5]	5
Model performance	23a	D;E	Report model performance estimates with confidence intervals, including for any key subgroups (e.g., sociodemographic). Consider plots to aid presentation.	4, 5
	23b	D;E	If examined, report results of any heterogeneity in model performance across clusters. See TRIPOD Cluster for additional details[3].	N/A
Model updating	24	E	Report the results from any model updating, including the updated model and subsequent performance	N/A
DISCUSSION				
Interpretation	25	D;E	Give an overall interpretation of the main results, including issues of fairness in the context of the objectives and previous studies	6
Limitations	26	D;E	Discuss any limitations of the study (such as a non-representative sample, sample size, overfitting, missing data) and their effects on any biases, statistical uncertainty, and generalizability	6
Usability of the model in the context of current care	27a	D	Describe how poor quality or unavailable input data (e.g., predictor values) should be assessed and handled when implementing the prediction model	6
	27b	D	Specify whether users will be required to interact in the handling of the input data or use of the model, and what level of expertise is required of users	6
	27c	D;E	Discuss any next steps for future research, with a specific view to applicability and generalizability of the model	6

From: Collins GS, Moons KGM, Dhiman P, et al. *BMJ* 2024;385:e078378. doi:10.1136/bmj-2023-078378

[4] This relates to the analysis code, for example, any data cleaning, feature engineering, model building, evaluation.
[5] This relates to the code to implement the model to get estimates of risk for a new individual.