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Artificial Intelligence in Brain Informatics

Predictive value of clot imaging in acute ischemic stroke: A systematic review of artificial intelligence and conventional studies

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ABSTRACT

The neuroimaging signs of the clot in acute ischemic stroke are relevant for clot biology and its response to treatment. The diagnostic and predictive value of clot imaging is confirmed by conventional studies and emerges as a topic of interest for artificial intelligence (AI) developments. We performed a systematic review to evaluate the state of the art of AI in clot imaging, how far AI is from becoming clinically beneficial, and what are the perspectives to consider for further developments. In parallel, the review is examining the evidence brought by conventional studies concerning the relevance of clot imaging, from 2019 to August 2022. The automatic detection and segmentation of the clot are the most important advances towards AI implementation in the clinic. Predictive radiomics models require further exploration and methods optimization. Future AI approaches could consider conventional clot imaging characteristics and patient specific vascular features as variables for model development.

1. Introduction

Artificial intelligence (AI) becomes recognized for its applications in medical field. AI methods are designed to harvest information from medical imaging, in the context of various diseases, with the purpose of rapid and accurate diagnosis and prognosis. Stroke is a condition requiring prompt intervention and carries high morbidity and mortality rates [1] [2] [3]. Various AI methods were developed based on information provided by computed tomography (CT) and magnetic resonance (MR) neuroimaging. The emerging applications of AI in stroke are examined in numerous recent reviews [4] [5] [6] [7] [8] [9] [10] [11] [12]. Often covered are AI developments that aim to differentiate between hemorrhagic stroke, ischemic stroke and stroke mimics, measure the Alberta Stroke Program Early CT Score (ASPECTS), detect and segment parenchyma, analyze the collateral flow status, detect large vessel occlusion (LVO) from computed tomography angiography (CTA), or analyze biomarkers of corticomotor structure and function. The image-based AI methods aim to have a powerful impact in clinical management of stroke, by improving the diagnostic, predictive and prognostic value of clinical neuroimaging. Various AI software received FDA (Food and Drug Administration) approval and CE (Conformité Européene) mark, although more evidence is necessary to prove in what degree they are clinically beneficial [12].

A growing number of articles are evaluating AI techniques that analyze the neuroimaging signs of the clot (or thrombus) occluding the arteries in ischemic stroke [13] [14] [15] [16] [17] [18] [19] [20] [21] [22] [23]. No systematic reviews were conducted so far to examine the progress made in developing AI methods that are using clot imaging derived parameters. The **aim** of our systematic review is to provide an overview regarding the advances made in extracting meaningful information from clot imaging with AI techniques, to understand how far AI is from becoming clinically beneficial, and what are the perspectives to consider for future developments. Because clot imaging continues to be investigated by research studies using conventional statistics, we also provide an overview of the recent findings in the field, with the aim of highlighting clot characteristics which are predictive for various aspects

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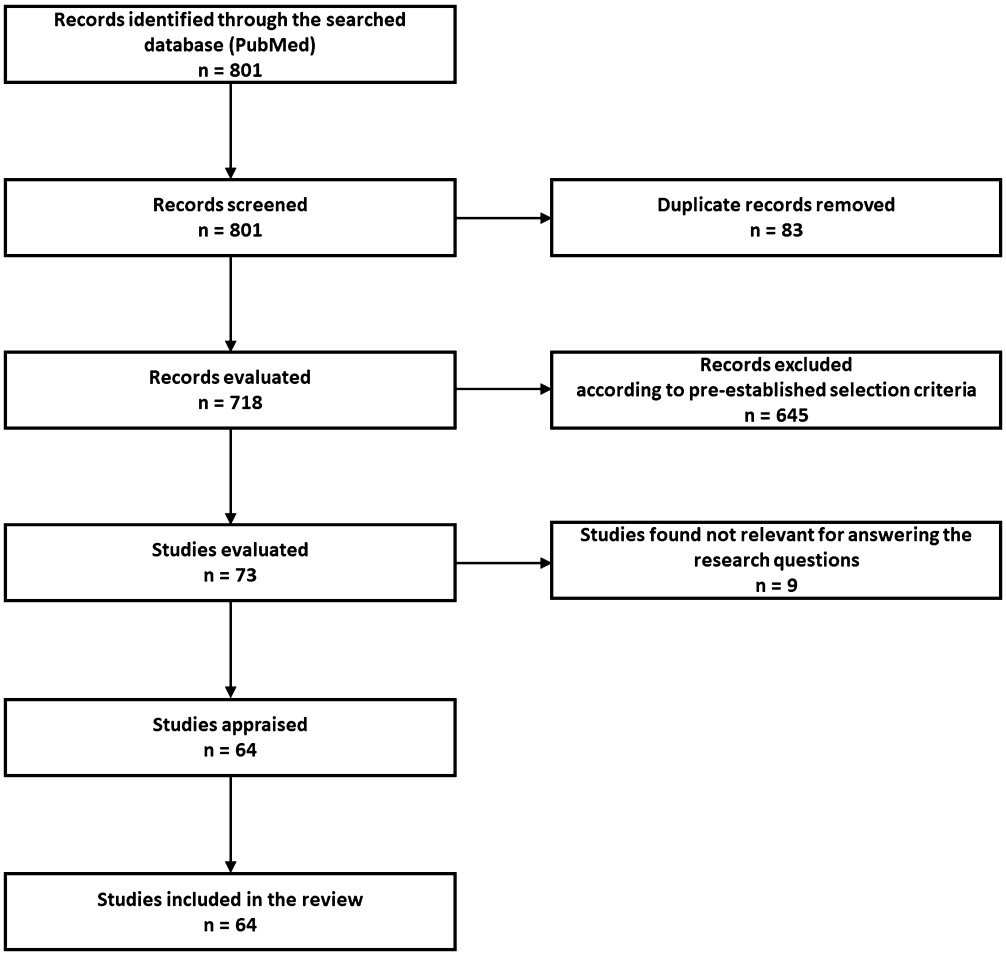

Fig. 1. Chart illustrating the selection process for studies included in the review.

in ischemic stroke and which can be proposed as variables for future AI predictive models.

2. Methods

A systematic review was performed according to PRISMA guidelines using PubMed resource, for all peer reviewed articles in English using predetermined search terms: "clot", "thrombus", "stroke", "CT", "MRI", "segmentation", large vessel occlusion", "vessel sign", "thrombectomy", "artificial intelligence", and combinations of them. Studies were included if they reported findings regarding the use of artificial intelligence algorithms in relation to imaging thrombus characteristics, using CT or magnetic resonance imaging (MRI), in ischemic stroke patients (AI studies), or if they used conventional statistics to answer a clinical research question and analyzed clot imaging characteristics, as observed in CT or MRI. Studies that resulted from these search criteria were excluded if they were published before 2019, because we wanted to avoid redescribing well-known findings of conventional studies, and because we found this time frame relevant for the AI studies. Studies were also excluded if the full text was unpublished, or if they did not report patient imaging (such as studies reporting ex vivo or in vitro results only, or animal studies).

Studies were extracted by a single author and reviewed by three authors independently. Data extraction was performed according to a pre-designed protocol (details provided in Supplementary material). Studies were classified according to their methods: AI studies, using AI algorithms, and conventional studies, using conventional statistics (including studies using logistic regression analysis in a conventional frame). The present review protocol is not a registered protocol. The last date for which the sources were searched was August 2nd, 2022. The quality of AI studies was evaluated according to the Checklist for Artificial Intelligence in Medical Imaging (CLAIM) [24], as presented in Supplementary material Table S1. The risk of bias in each individual study was assessed according to Newcastle–Ottawa Scale [25] (Supplementary material Table S2). Wide variability in design and statistical calculations of the reviewed studies prevented calculation of principal summary measures.

3. Results

The study selection process is illustrated in Fig. 1. The distribution of the studies included in the review, according to their purpose and methods (imaging techniques, variables included in the analysis) is presented in Fig. 2.

We provide in the Results section the following: an overview of radiomics models using clot imaging features, a summary of the studies reporting automatic segmentation of the clot and automatic detection of the clot, the findings of conventional studies evaluating predictors derived from clot imaging, and insights into the variability of thrombi according to CT characteristics.

4. Clot radiomics for predicting thrombus composition and response to treatment

The biological nature of the clot, which consists specifically in its composition and organization, does affect the response to treat-

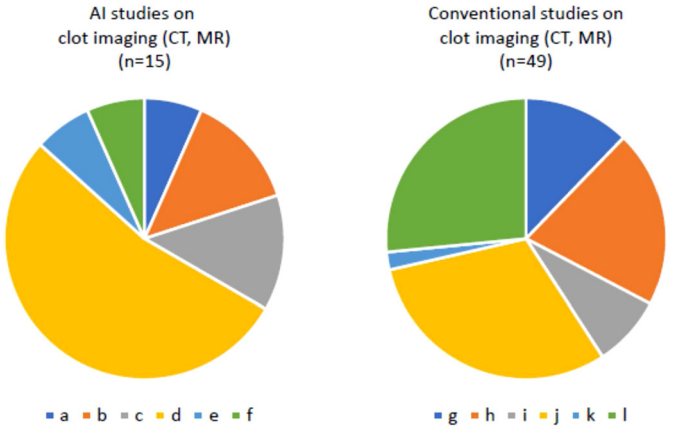

Fig. 2. Distribution of studies using AI for the analysis of clot imaging and distribution of conventional studies focused on the significance of clot imaging, based on study aim and methods, from 2019 to August 2nd 2022. **AI studies**: a- models predictive for thrombus composition from CT; b- models predictive for recanalization outcome from CT; c- models predictive for recanalization outcome from CT and included clinical variables; d- models for automatic detection and segmentation of thrombus on NCCT; e- models predictive for thrombus composition from MRI; f- clustering of thrombi according to CT characteristics. **Conventional studies**: g- evaluating CT markers for thrombus composition and organization, and CT predictors for clinical outcomes; h- evaluating CT markers for thrombus composition and organization, and CT predictors for clinical outcomes, including in the analysis clinical variables; i- evaluating CT predictors for clinical outcomes; j- CT predictors for clinical outcomes, including in the analysis clinical variables; k- evaluating MR markers for thrombus composition and organization, and MR predictors for clinical outcomes, including in the analysis clinical variables; l- evaluating MR predictors for clinical outcomes, and including in the analysis clinical variables.

ment, whether it is thrombolysis or mechanical thrombectomy. An important endeavor for clinical neuroimaging in stroke is obtaining information regarding the clot composition from patient imaging scans, and to predict the response to treatment. Nevertheless, the clot imaging made the subject of several studies that extracted and analyzed quantitative features from CT scans – Table 1 (detailed extracted data is presented in Supplementary material Table S3).

One study, which developed machine learning algorithms capable of recognizing thrombus composition [13], used imaging data obtained with thin slice non contrast CT (NCCT) and CTA. After performing a semi-automatic delineation of the thrombus, Hanning et al. [13] extracted a large number of quantitative image markers (radiomic features) per thrombus and established a machine learning based classifier for predicting thrombus composition. The classification in this proof-of-concept study is based on RBCs/fibrin cut-off values corresponding to arbitrarily chosen quantiles. The study emphasizes the importance of various and multiple predictive quantitative imaging features. Along with features from thrombus and vessel wall segmentation, the model is using features extracted from the regions of perivascular tissue, which proved to be important predictors for fibrin rich thrombi, isodense in NCCT.

There are also studies that use the clot radiomic features (RFs) to train and validate models predictive for treatment outcome. Among them, the study of Qiu et al. [14] uses the selected features to train a linear support vector machine classifier for predicting early recanalization after administration of IV alteplase. The study of Hofmeister et al. [15] utilizes a support vector machine classifier to train and validate a model predicting first-attempt recanalization with thromboaspiration, and a support vector regression to train and validate a model predicting the number of passages required for successful recanalization with stent retriever. The study of Sarioglu et al. [16] utilizes the selected RFs as variables in a logistic regression model, along with demographic and clinical variables, and van Voorst et al. [17] compares the predictive performance of random forest models using either a set of 6 thrombus radiomic features, a set of 19 clinical variables, a set of 3 manually extracted thrombus measurements (density, perviousness, thrombus length), or combinations of these sets of variables.

The studies use datasets of various sizes (as listed in Table 1) and each extract a different number of RFs per thrombus. The procedures for selecting the relevant RFs, which are used in model development, differ vastly among the studies, and the number of RFs identified as predictive is different. Not surprisingly, for studies considering additional predictor variables, along with RFs, the findings are also very different: Qiu et al. found RFs more predictive than conventional CT derived measures of thrombus [14], Sarioglu et al. found that the diagnostic accuracy is increased when combining RFs with demographic and clinical variables [16], and van Voorst et al. [17] found that random forest models using thrombus radiomics, clinical variables or manual thrombus measurements have comparable predictive performance.

The studies that investigate clot radiomics do not hold generalizable value. Some are single-center studies [13] [15] [16], or use a small sample size [14], and merely establish a proof-of-concept for models predictive for thrombus characteristics or various treatment-related outcomes. Compared to the other studies, van Voorst et al. [17] is using a larger data set while extracting a relatively low number of RFs per thrombus. The generalizability of his findings is hampered by the lack of comparison with radiomics models evaluating different sets of RFs.

Contrary to the attention received by the CT of the clot for extracting quantitative image markers and training machine learning models, the MRI of the clot remains vastly unexplored. An AI study used images acquired with gradient echo sequences (GRE) at 3T MRI to establish a machine learning model capable of predicting the atrial fibrillation (AF) as origin of thrombus [26] (Supplementary material Table S4). The model extracted signal graphic information from one dimensional sectional profiles manually drawn over regions of interest in MRI scans and used binary labeling (AF and non-AF) to train a machine learning classification model.

5. Automatic detection and segmentation of the clot

Some studies indicate that when the thrombus is distinguishable on NCCT, its hyperdense sign and location can be used, without the acquisition of additional brain scans, to rapidly recognize the eligibility for thrombectomy. As such, a recent study [27] which compared the NCCT findings with DSA, CTA and MRA in terms of thrombus detection, indicated that on thin slice NCCT a hyperdense artery sign corresponding to middle cerebral artery (HMCAS) can be enough to decide on transfer for thrombectomy in drip-and-ship models. Another study even indicated that the hyperdense artery sign can be used to guide the choice of thrombectomy device (stent retriever vs. contact aspiration) [28]. The potential clinical benefit derived from early HMCAS detection triggered AI developments. We identified 6 studies concerned with the automatic detection of the occlusion from NCCT (Table 2, and more detailed information in Supplementary material Table S5) [18] [23] [19] [20] [21] [29]. A recent large AI study, using a historical database of 24214 patients for training and 1453 patients for validation, established a machine learning algorithm and a software (MethinksLVO) [18] capable of rapidly and reliably predicting LVO from NCCT scans with slice thickness 3-to-5 mm. Weyland et al. [23] tested a readily available software, Brainomix © (Oxford, UK). Shinohara et al. developed [19] and tested [20] an interactive deep learning-assisted identification of HMCAS, on NCCT. Because of the small sample size of image data, Shinohara et al. [19] used data augmentation methods, which yielded 252 image samples per CT scan. Two of the studies [29] [21] also elaborated methods for the automatic segmentation of thrombi detected in NCCT.

In addition, we identified two studies [22] [30] elaborating automatic segmentation of thrombus using information from NCCT

Table 1
Summary of articles evaluating clot radiomics from CT scans.

Author, year of publication	Target variables	Study design	Number of extracted RFs per thrombus	Number of predictive RFs reported	Findings
Hanning et al., 2021 [13]	Binary: 1) RBCs rich (lower third quantile of fibrin/RBC ratio), vs others thrombi 2) fibrin rich (upper third quantile of fibrin/RBC ratio), vs others thrombi	Single center retrospective 122 patients	4844 RFs	100 RFs	Machine learning based analysis of admission imaging allows for prediction of clot composition
Qiu et al., 2019 [14]	Binary: recanalization after administration of IV alteplase	Multicenter 67 patients, nested case-control design (30 patients and 37 controls matched for age, sex, and stroke severity)	326 RFs	12 RFs	Thrombus radiomics features are more predictive of recanalization with IV alteplase than previously known thrombus imaging features such as length, volume, and permeability.
Hofmeister et al., 2020 [15]	1) Binary: successful recanalization 2) Continuous: number of thrombectomy passes	Single center 156 patients n = 109 in retrospective training cohort; n = 47 in prospective validation cohort	1485 RFs	9 RFs	9 RFs were predictive of first-attempt recanalization with thromboaspiration and also predicted the overall number of passages required for successful recanalization
Sarioglu et al., 2022 [16]	Binary: FPE	Single center retrospective 52 patients 25 FPE cohort, 27 non-FPE cohort	88 RFs	2 RFs	2 RFs were independent predictors of FPE, in addition to female sex and a baseline ASPECTS of >8.5.
Van Voorst et al., 2022 [17]	Binary: 1) successful reperfusion (eTICI $\geq$ 2b), 2) first attempt reperfusion eTICI $\geq$ 2b, 3) reperfusion (eTICI $\geq$ 2b) within three attempts 4) functional independence (mRS $\leq$ 2)	Multicenter retrospective 699 patients n = 499 training cohort for random forest models; n = 200 testing cohort, for ordinal regression analysis	107 RFs	4 RFs	Random forest models using RFs, clinical variables or manual thrombus measurements had comparable predictive performance.

ASPECTS = Alberta Stroke Program Early CT Score; eTICI = expanded treatment in cerebral infarction; FPE = first pass effect of mechanical thrombectomy (mTICI 2c/3 at first pass); mRS = modified Rankin scale for neurological disability; MTB = mechanical thrombectomy; RFs = radiomic features.

and CTA combined (Table 2, and Supplementary material Table S5). Mojtahedi et al. [22] used an off-the-shelf algorithm, StrokeViewer LVO (Nicolab, Amsterdam, The Netherlands), to first detect the thrombus location. The study developed a segmentation method based on a bounding box algorithm and CNN, capable of segmenting thrombi even when the contrast difference between hyperdense artery sign (HAS) and background is minimal. Including CTA in addition to NCCT improved thrombus segmentation accuracy and allowed to distinguish hyperdense areas that mimic HAS. The method was designed as such that it can be applied independently of the procedures used in the first step for thrombus localization. Zoetmulder et al. [30] aimed to elaborate a method capable of accomplishing detection and segmentation of thrombi in posterior circulation stroke (PCS), by restricting the volume of interest to areas in the vicinity of the brainstem. The method was not accurate for localizing and segmenting thrombi in the vertebral and posterior cerebral artery but did achieve a good localization precision and a reasonable segmentation accuracy for thrombi in the basilar artery, the most common location for PCS.

6. Predictive value of clot imaging in conventional studies

Recent AI studies consider conventional clot characteristics obtained from CT scans, such as density, perviousness, length [14] [17]. Recent advancements in automatic segmentation methods open vast possibilities for exploration of clot neuroimaging signs. For these reasons, we feel compelled to examine the current state of the art of the predictive value of the clot imaging, as reflected in conventional studies. The rationale for this investigation is based on the need of understanding the current limitations in the field, and on providing a background for extrapolation of meaningful variables into the development of AI predictive models in ischemic stroke.

6.1. Markers associated with clot composition

Several studies investigate associations between CT imaging markers and thrombus biological nature, which is evaluated with various methods (Supplementary material Table S6). Two types of thrombus imaging markers emerge from conventional: markers describing the attenuation properties of the clot, responsible for its density on NCCT, and markers describing the permeability of the clot for the contrast agent (Table 3). Histopathological evaluation is the gold standard for describing thrombus composition. Some studies use for this purpose human evaluation (by expert pathologists) [31] [32] [33], other studies use for quantification Orbit Image Software analysis [34] [35] [36] [37] [38] [39], and one study compared the histopathological evaluation performed by the expert pathologists with the performance of the Orbit Image Software analysis [40]. The latter found that quantification of thrombus composition using the software allowed finding significant associations which were not found using the reference method. When using Orbit software, the histological content of thrombus is described with quantitative variables (RBCs, fibrin, platelets, and WBCs in %). Evaluation by expert pathologists describes thrombus composition in categorical variables (red, mixed and white categories [31], or red non-organized and white organized [32]). Decreasing the NCCT slice thickness is known to increase the sen-

Table 2
Summary of studies concerned with automatic segmentation and thrombus detection on NCCT.

Author, year of publication	Scope of study	AI method	CT technique	Number of centers, Sample size (n, number of patients), allocation	Findings
Olive-Gadea et al., 2020 [18]	identify LVO on NCCT	MethinksLVO software	NCCT thickness 3-5 mm	2 comprehensive stroke centers n = 24 214 patients in training cohort, from historical database n = 1453 validation cohort (CTA as reference)	MethinksLVO software can rapidly and reliably predict LVO Sensitivity 0.83 Specificity 0.71
Weyland et al., 2022 [23]	HAS (LVO) detection	commercial software Brainomix	NCCT (slice thickness ≤1 mm)	Three centers n = 154, n = 84 with and n = 70 without LVO proven by CTA	Sensitivity 0.77 Specificity 0.87 Performance similar to expert neuroradiologists
Shinohara et al., 2020 [19]	HMCAS detection on NCCT	CNN (Xception)	NCCT 0.46-mm in-plane resolution	From n = 22 patients: 35 HMCAS-positive and 39 HMCAS-negative imaging samples, followed by data augmentation	Sensitivity 0.83 Specificity 0.90 Model potentially beneficial
Shinohara et al., 2020 [20]	HMCAS detection on NCCT	CNN (Xception)	NCCT 0.46-mm in-plane resolution	n = 79 patients: 46 HMCAS-positive and 52 HMCAS-negative test image samples	Sensitivity 0.82 Specificity 0.80 Performance similar to expert neuroradiologists
Tolhuisen et al., 2020 [21]	HAS detection and thrombus segmentation on NCCT in patients with LVO	CNN	NCCT Slice thickness ≤2.5 mm	Multicenter n = 86 for training n = 43 for validation For testing: n = 58 with LVO and n = 45 without LVO (CTA as reference for LVO)	Sensitivity 0.86 Specificity 0.65 Performance similar to expert neuroradiologists
You et al., 2021 [29]	HMCAS detection and segmentation on NCCT	deep DSU-Net	NCCT multiple scanners, various slice thicknesses	Multicenter n = 624 for training, n = 324 for validation	Accuracy of HMCAS detection 0.86, Specificity 0.92 Detection and segmentation performance similar to expert neuroradiologists
Mojtahedi et al., 2022 [22]	Segmentation of thrombus from NCCT and CTA combined, in patients with ICA-T, M1 and M2 occlusions	StrokeViewer LVO dynamic bounding box algorithm CNN	NCCT CTA multiple scanners, various slice thicknesses	Multicenter n = 208 training cohort n = 20 validation cohort n = 100 in testing cohort	Overestimation of the volume of small thrombi and underestimation of the volume for larger thrombi by the automated segmentations, compared to the ground truth, with an overall high spatial overlap with the manual annotation by expert neuroradiologist used as ground truth. Dice coefficient 0.62 Surface dice 0.78 (Performance based on the sensitivity of StrokeViewer for LVO, 0.78)
Zoetmulder et al., 2022 [30]	thrombus localization and segmentation on co-registered NCCT and CTA, in patients with PCS	CNN (Polar-UNet)	NCCT CTA co-registration	Multicenter n = 187 patients	A good localization precision and a reasonable segmentation accuracy for thrombi in the basilar artery Dice coefficient 0.44

CNN = convolutional neural network; CTA = CT angiography; DSU-Net = Dissimilar-Siamese-U-Net; HAS = hyperdense artery sign; HMCAS = hyperdense middle cerebral artery sign; ICA-T = terminal internal carotid artery; M1, M2 = occlusion sites in middle cerebral artery (MCA); LVO = large vessel occlusion; NCCT = non-contrast CT; PCS = post circulatory stroke.

sitivity for hyperdense arterial sign (HAS) detection and improve the prediction of thrombus histopathology [41] [38]. Although the NCCT slice thickness varied among the studies, as well as the type of variables used to describe thrombus composition, most studies [40] [34] [31] [36] [38] [42] [43] confirmed statistically significant associations between the hyperdense sign of thrombus on NCCT and RBCs rich content, or between HAS absence and the platelets or fibrin content. Recently, a study indicated that predicting thrombus composition is multifactorial: combining HAS with occlusion location, thrombus length, and variables derived from CTA scans increased the predictive value for RBCs rich thrombi and explained up to 30% of variability in RBCs content [38].

Meanwhile, the studies assessing perviousness measures report divergent findings. Some studies explored the associations between thrombus composition, described with histopathological evaluation, and the clot perviousness [35] [36] [37], described by throm-

Table 3
Summary of articles investigating associations between CT derived variables and thrombus composition or porosity.

Studies grouped by main findings	Study methods			
	Categorical variables for thrombus composition or porosity, NCCT thick slice (typically 5 mm)	Categorical variables for thrombus composition, thin slice NCCT ($\leq$ 2.5 mm)	Continuous variables for thrombus composition, NCCT thick slice (typically 5 mm)	Continuous variables for thrombus composition, thin slice NCCT ($\leq$ 2.5 mm)
Studies confirming associations between NCCT hyper density and thrombus RBCs rich composition or decreased fibrin and/or platelets composition (using conventional statistics)	[40]	[31]	[34]	[36] [38] [42] [43]
Studies finding no associations between NCCT density and thrombus composition	-	-	-	[37]
Studies finding an association between the increased perviousness measures (TAI) and increased content in RBCs or decreased content of fibrin/platelets, or lack of association of perviousness with cardioembolic origin	-	-	-	[35] [36] [44]
Studies finding an association between the increased perviousness measures (TAI or TES) and decreased content in RBCs or increased content of fibrin/platelets, or association of perviousness with cardioembolic origin	-	-	-	[37] [39] [45] [33]
Studies finding an association between the increased perviousness measures (TAI), decreased content in polyhedral RBCs and increased porosity, but no association between TAI and overall RBCs content.	[46]	-	-	-

bus attenuation increase (TAI), which measures the difference in density of the clot in CTA compared to NCCT. Other studies used the thrombus enhancement sign (TES) on CTA to describe the permeation of the contrast agent in the region of the vessel occupied by the occluding clot [39] [33]. There are also studies investigating associations between perviousness and stroke etiology, based on TOAST criteria. It is known that thrombus composition varies according to stroke etiology, with cardioembolic thrombi being rich in fibrin and lower in RBCs content [47] [48] [49]. Two studies investigate the associations between TAI and the cardioembolic vs large artery atherosclerosis (LAA) etiology, and report different findings for different occlusion locations (proximal middle cerebral artery occlusions vs. basilar artery occlusions) [45] [44], and one study investigates correlations between TES and stroke etiology [33]. Characterizing thrombi porosity is a subject of exploration. One study [39] used scanning electron microscopy (SEM) to categorize thrombi according to their porosity, to evaluate the shape of RBCs, the fibrin organization, to estimate thrombus composition and investigate associations with thrombus perviousness.

The explanations for the divergent findings concerning the associations between the perviousness measures and thrombus composition are multifold. The studies summarized in Table 3 differ in regard with the thrombolytic treatment administration. Two studies [37] [39] excluded from the analysis patients that received thrombolytic treatment. Meanwhile, 34% of the patients included in [33], all included patients in [35], and 28% of the patients included in [36] received thrombolytic treatment prior endovascular treatment, fact that could have altered the relevance of histopathological evaluation in correlation with CT imaging. A second explanation could stem from the fact that thrombus perviousness being, in principle, a measure of the flow passage, and therefore a reverse measure of thrombus compactness, is affected by underlying biological features which are neither completely understood nor measurable with the currently available experimental methods. Such features are the degree of intravital contraction [48] [50] [51] [52], and the morphology and the organization of fibrin network, which depend on the blood flow conditions during thrombus formation [50] [52] [53]. An attempt to link thrombus perviousness to more adequate biological features, such as porosity and the compactness of RBCs, is made by He et al. [46], although the study does not mention if patients received thrombolytic therapy. A third explanation stems from the variability of anatomical specificities related to occlusion location and local blood flow conditions. This could partially explain the different findings between the studies that selectively included patients with occlusions at a specific (and different) site only [45] [44], and the studies which included patients with occlusions at various locations, in various proportions [35] [36] [37] [39] [33]. In conclusion, the biological substrate for thrombus perviousness measures is not completely understood, and not adequately described in research studies. The perviousness measures are not markers of thrombus composition, but rather markers of thrombus organization, in the context of local hemodynamics.

Some of the above-mentioned studies [36] [32] [39] [44], and in addition others, which did not perform a histological analysis of the retrieved clot [37] [54] [55] [56] [57] [58] [59] [60] [61] [62] [63] [64] [28] [65] [66] (Supplementary material Table S7), explored associations between imaging markers for thrombus biology and clinically relevant, treatment related, metrics. The distribution of these studies is presented in Table 4. Some studies found no associations between thrombus imaging markers and clinical aspects such as hemorrhage occurrence following treatment [54] [63], or successful recanalization [36] [37] [44] [55], number of stent retriever passes [55], embolization [32] [55], while other confirmed various associations [39] [56] [57] [58] [59] [60] [61] [62] [64] [28] [65] [66] [67].

There are similarities and differences among the two groups of studies, A and B in Table 4. The two groups contain a similar distribution of studies in terms of frequency of using thin slice CT (at least 5 out of 8 in Group A, and at least 9 out of 13 in Group B

Table 4
Account of conventional studies investigating associations between CT thrombus density or perviousness measures and outcomes in ischemic stroke treatment or treatment strategy.

Reported findings	Clot related CT derived variables	Outcomes				
		Recanalization outcome following treatment (iv tPA or MT)	Functional recovery, or neurological improvement	Embolization following treatment	Hemorrhage following treatment	Treatment strategy
no associations found between CT derived variables and outcomes (group A of studies)	Density derived variables (on NCCT)	[36] [37] [55]	[31] [36] [32] [63]	[32] [55]	[63]	[55]
	Perviousness related variables	[36] [37] [44] [55]	[36] [44]	[55]	[54]	[55]
associations found between CT derived variables and outcomes (group B of studies)	Density derived variables (on NCCT)	[59] [60]	[60] [64] [67]	[56] [58]		[58] [28] [64]
	Perviousness related variables	[39] [57] [61] [62] [65]	[61]			[65] [66]

used thin slice CT), and in terms of including in the statistical analysis, along with CT derived variables, clinical variables (6 out of 8 studies in A, all 13 studies in B). There are nevertheless differences between the two groups. In Group B, 5 out of 13 studies consider predictors such as thrombus extent (CBS, or thrombus volume or length) [56] [57] [62] [65] or vessels anatomy configuration [59]. In group A one out of 8 studies considers thrombus extent as predictor [54]. Importantly, studies in Group B used significantly larger sample sizes than studies in Group A (Supplementary material). Overall, studies in group B are more robust, and their results more reliable.

In regard with MRI markers of thrombus composition, older studies are associating the susceptibility vessel sign (SVS), in T2* GRE or susceptibility weighted imaging (SWI), with increased RBCs content [68]. Recently, Darcourt et al. [69] indicated the clots that do not display SVS are rich in fibrin/platelets, less likely to be retrieved by aspiration alone and more often require the use of combined therapy. The thrombus susceptibility from SWI mapping was found to be weakly and negatively correlated with diffusion weighted imaging (DWI)-ASPECTS, and weakly and positively correlated with National Institutes of Health Stroke Scale (NIHSS) at admission and discharge [70]. The presence of SVS was found to be one of the predictors of excellent outcome in patients with LVO treated with intravenous (IV) tissue plasminogen activator (t-PA) alone [71], and to be associated with successful reperfusion after mechanical thrombectomy [72] [73], although superior clinical functional outcome and lower mortality could not be entirely attributed to higher reperfusion rates [73]. In patients receiving first-line stent retriever treatment, SVS was associated with lower disability at 3 months [74]. Also, it was shown that the probability of the SVS sign increases with time from symptom onset, and factors independently associated with SVS positive status were type of MRI scanner, cardioembolic cause and baseline NIHSS [75]. A detailed account of these studies is provided in Supplementary material Table S8. As evidence shows, the SVS sign is amply considered by conventional MRI studies as marker of the clot. Although the evidence is scarce, other sequences are being investigated as well: a recent study suggests that the bright vessel sign on arterial spin labeling (ASL BVS) is more sensitive for identification of LVO, when superposed with either MRA or DSA, compared to GRE SVS [76].

6.2. Clot extent, location and shape

Information about the extent of thrombus is typically obtained from angiographic scans, CTA or MRA, according to a scoring system known as clot burden score (CBS) [77] [78]. Some studies also measure thrombus length by evaluating the extent of HAS in NCCT, or the extent of the SVS sign in T2* GRE or SWI MRI sequences. Thrombus extent is relevant in many aspects.

Increased thrombus length and lower CBS were associated with non-cardioembolic stroke etiology [79]. Quite contrary, SVS length and admission matrix metallopeptidase 9 (MMP-9) serum level were found to improve the prediction of cardioembolic stroke when its profile is close to embolic stroke of undetermined source, which suggests a common cardiac embolic source [80]. CT-derived thrombus characteristics, CBS and thrombus length, were also found similar for cardioembolic strokes and strokes with undetermined origin [79]. Thrombus length was found to be a strong predictor of RBCs content [38].

Longer thrombus was associated with distal embolization [32] [55], and lower CBS was found in univariate analysis to be a risk factor for secondary embolization [56]. A CBS $\leq$3 robustly predicted postprocedural hemorrhage [54].

Lower thrombus extent was found to be critical for the effectiveness of IV-tPA [57] and associated with early recanalization following IV-tPA treatment [81], and thrombus length was found a powerful independent predictor of no-early recanalization following IV-tPA treatment in minor strokes [82]. Short SVS was found to be a predictor of excellent outcome at 3 months in patients with stroke with LVO treated with IV-tPA alone [71].

CBS was higher in patients with mild stroke, compared with patients with severe stroke [62]. The SVS length was weakly and negatively correlated with DWI-ASPECTS, and CBS was weakly and positively correlated with DWI-ASPECTS, and weakly and negatively correlated with admission and discharged NIHSS [70].

CBS was found to be an independent predictor of short and long-term functional outcome [83], with rate of favorable outcome increasing with CBS [84]. In patients with minor stroke (NIHSS $\leq$4 within 24 h following onset) longer SVS was associated with increased risk of early neurological deterioration, and SVS $\geq$ 9.45 mm was a powerful independent predictor of early neurological deterioration [85].

Occlusion location, measured as distance from ICA terminus to thrombus beginning, is another relevant parameter. It was found that the occlusion location is a predictor for RBC content [38], and it is associated with postprocedural hemorrhage [54]. Early recanalization following IV-tPA treatment was associated with more distal occlusion [81]. As compared with patients with severe stroke, patients with mild stroke had more distal occlusions [62].

In addition to thrombus density, perviousness, extent, and distance from internal carotid artery (ICA) terminus, also the shape of the clot plays, according to some studies, a role onto the treatment efficacy. A significantly lower rate of successful reperfusion was found in patients with angulated or bifurcated SVS, vs patients with straight SVS [86]. Combinations of MRI sequences were found helpful for treatment planning in case of bifurcated thrombi: the high spatial resolution of 3D turbo spin echo (3D TSE) T1-weighted was useful for identifying thrombus location, and 3D TSE T2-weighted depicted clearly the arterial configuration [87]. A recent retrospective study [88], using data from MR CLEAN registry,

casts doubt whether a more aggressive endovascular treatment approach is justified for MCA bifurcated occlusions, compared to MCA main-stem occlusions. However, the study suffers from the oversimplification of the complex occlusions patterns that can be found in patients.

7. Using AI to classify thrombi according to CT characteristics

Recently, a study using the MR CLEAN Registry dataset used unsupervised clustering with the purpose of grouping thrombi based on the CT image findings according to 1) occlusion location and 2) thrombus length, density and perviousness [89] (Supplementary material Table S5). The study found that thrombus imaging characteristics form a continuum spectrum, in which a given single thrombus variable is accompanied by a large variety of other characteristics, and as such, grouping thrombi in archetypes is not adequate. The study emphasizes the large variability of thrombi, a paradigm that replaces the composition-based categorization and has large implications onto future approaches in treatment design and elaboration of predictive models based on clot imaging interpretation.

8. Discussions

The automatic segmentation of the clot is probably the most important advancement made by AI for reaching an improved output from clot imaging. Its applications are multiple. On one hand, rendering 3D information about the clot in CT or MRI scans could help accelerate the research performed by the large body of conventional studies. It has been shown that the automatic segmentation of entire thrombus allows obtaining measures with a stronger association with clinical outcomes, compared to the manual assessments using regions of interest (ROIs) [61]. Because of the unavailability of automatic segmentation methods, and because the manual segmentation of the clot is a tedious process, conventional studies resort so far to manual delineation of ROIs, in CT scans slices, to read the density values and to provide image markers associated with clot composition and organization, such as the HAS and perviousness measures. Disposing of standardized means, across multiple centers, of gathering comprehensive information about the clot through 3D renderings could not only provide accurate, meaningful variables for conventional studies, but also accelerate AI developments [17]. In perspective, clot characteristics obtained from automatic 3D renderings could be used as variables for training AI models predictive for clot composition and response to treatment: along with measures of density and perviousness, the clot extent and shape, together with its location, can provide a wealth of information.

Furthermore, all the radiomics studies of the clot relied so far on manual segmentation as well, fact that limited the progress in the field. Access to automatic segmentation could accelerate the development of clot radiomics [15], improve uniformity among studies, facilitate inclusion of large and multicenter data sets and, as a consequence, the development of radiomic models with generalizable value.

Not at last, automatic segmentation of thrombus could help, in the future, guide endovascular treatment. When obtained rapidly before thrombectomy, 3D representations of the clot in the context of patient specific vascular anatomy could help the interventionalist become aware of the clot positioning relative to branching arteries, and as such provide him the necessary information for optimal deployment of stent retriever.

Nevertheless, the optimal automatic segmentation of entire population of thrombi is still facing technical challenges, and it should include isodense thrombi, small thrombi and thrombi located at less frequent arterial sites [22] [30].

Currently, the automatic LVO detection with image-based AI is available through CTA scans. Among the FDA approved and CE marked software are, for example, RapidLVO (iSchemaView, Inc.), with a sensitivity of 97%, and Viz LVO (Viz.ai, Inc.) with a sensitivity of 96%. Algorithms for hyperdense artery sign detection support a new paradigm in stroke care, which is based on the direct to angiography (DTA) model. The model intends to reduce the delays in initiating treatment when they are associated with additional and unnecessary neuroimaging investigations. Most likely, benefitting from this model are predominantly the patients with severe stroke (NIHSS $>$ 9) in early time window (0-6 h hours from symptoms onset) [90]. Several studies published up to date demonstrate the feasibility of automatic hyperdense sign detection and its translational potential. Among the published data, MethinksLVO software (Methinks AI, Barcelona, Spain) is nearing clinical applicability [18] [91]. The software is capable of detecting LVO on NCCT in less than two minutes, with sensitivity superior to the one provided by preexisting scales [92], or proposed by an artificial neural network model based on demographic and clinical variables [93].

Quantitative imaging features in CT and MR scans, inherently linked to thrombus intrinsic properties, have a vast and unexplored potential for predicting the response of the clot to treatment. More exploratory work is necessary in establishing AI models predictive for thrombus biology and its implications. The clinical utility of radiomics is delayed by well-known technical challenges [94] [95]. Currently there are not enough evidence and no methodology available that could help optimize the study design for clot radiomics, and the choice of models to be trained. The selection of radiomic features is far from standardization. Research shows that, because feature relevance depends on the used machine learning model [96], the radiomic features cannot become biomarkers. In perspective, multicenter studies comparing the performance of various AI models, using radiomic features and conventional clot related variables, can help render radiomics models effective and accelerate their access into the clinical use.

The clinical utility of AI predictive models can be limited by the predilection for developing machine learning models destined to perform binary classification. Nevertheless, some binary target variables can be useful, such as the first pass effect in endovascular treatment, the recanalization following IV-tPA administration, the embolization, or the hemorrhage following intervention with endovascular treatment. However, thrombi population spans a large variability [89]. Prediction of thrombi biology in terms of conventional composition categorization is of limited value, when spatial heterogeneity becomes recognized as an influencing factor for thrombus response to treatment [97]. Novel volumetric methods might help collect relevant information about the 3D organization of thrombi and provide volumetric quantitative variables [98] [99], which can add meaning to measures such as perviousness. Examining thrombi ex vivo and quantifying structural features responsible for how thrombi behave towards various thrombectomy devices might help define new and more relevant thrombi categories, which can be used as ground truth for machine learning classifier models. Moreover, the outcome of endovascular treatment in stroke is multifactorial. Besides the thrombus biology, there are anatomical factors and multiple procedural factors contributing to the outcome [11] [100]. Anatomical features such as the carotid tortuosity was often overlooked by studies up to date, and emerges as an important factor affecting the procedure and its success [59] [101] [102] [103]. The future of AI development can shift, in a first instance, from using radiomics to using more relible and accessible variables, when training and validating models predictive for various clinical outcomes. Especially when placed in the context of patient specific vascular anatomy, the clot location, extent and shape can be important predictors for endovascular treatment outcome. Having knowledge beforehand about these factors can

help design the intervention strategy, and future AI developments should address this need. Other variables that can be considered for future model developments are the conventional image characteristics: CT density and perviousness measures, MR susceptibility measures, when obtained not from ROIs, but from 3D representations of the clot. The clinical relevance of the MR imaging of the clot is demonstrated. In perspective, using postprocessing techniques, combining various MRI sequences or implementing new MRI sequences can help define new correlations between imaging findings and thrombus characteristics such as composition, etiology, compactness [104] [105] [106].

Clot imaging in acute ischemic stroke is clinically significant. It offers many incentives for developing AI models. However, there are several ethical and legal concerns, before AI can be used with full confidence in clinical practice [107] [108]. Around the world, regulatory agencies issued guidelines to help define best practices for AI development and deployment. In European Union, the guidelines list seven key requirements which AI systems must meet, throughout their entire life cycle, in order to be considered lawful, ethical and robust from technical and social perspective [109]. AI will be successfully implemented through the collaboration of all stakeholders in complying with the issued guidelines and in helping to perpetually improve the regulations. AI will, nevertheless, become an important instrument for clinicians and impact favorably the lives of patients but will not replace the human decision making.

Limitations of our review stem from the fact that the number of prospective studies available for review was limited, and from potential publication bias, because unpublished data was not included.

9. Conclusion

The automatic detection of the hyperdense sign on NCCT and the automatic segmentation of the clot are the most important advances up to date towards clinical utility of AI algorithms that are using clot imaging. Clot radiomics is in early stage, with exploratory steps being necessary before optimizing the methods for model development. Important parameters to consider for models predicting the outcome of endovascular treatment are the clot location, extent and shape, in the context of patient specific vascular anatomy. Future developments of predictive AI algorithms in ischemic stroke could include conventional variables derived from 3D representations of the clot, such as image markers for clot biology: density, perviousness measures in CT, susceptibility measures in MRI.

Human and animal rights

The authors declare that the work described has not involved experimentation on humans or animals.

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Author contributions

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DDL searched the database, selected the studies, extracted data, analysed data and wrote the original draft.
JH and AR reviewed the studies, extracted and validated data.
KOL and PM designed the study and acquired funding.
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Declaration of competing interest

The authors declare that they have no known competing financial or personal relationships that could be viewed as influencing the work reported in this paper.

Appendix A. Supplementary material

Supplementary material related to this article can be found online at https://doi.org/10.1016/j.neuri.2022.100114.

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