Automated Methods for Detecting and Quantitation of Enlarged Perivascular spaces on MRI

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The brain’s glymphatic system is a network of intracerebral vessels that function to remove “waste products” such as degraded proteins from the brain. It comprises of the vasculature, perivascular spaces (PVS), and astrocytes. Poor glymphatic function has been implicated in numerous diseases; however, its contribution is still unknown. Efforts have been made to image the glymphatic system to further assess its role in the pathogenesis of different diseases. Numerous imaging modalities have been utilized including two-photon microscopy and contrast-enhanced magnetic resonance imaging (MRI). However, these are associated with limitations for clinical use. PVS form a part of the glymphatic system and can be visualized on standard MRI sequences when enlarged. It is thought that PVS become enlarged secondary to poor glymphatic drainage of metabolites. Thus, quantitating PVS could be a good surrogate marker for glymphatic function. Numerous manual rating scales have been developed to measure the PVS number and size on MRI scans; however, these are associated with many limitations. Instead, automated methods have been created to measure PVS more accurately in different diseases. In this review, we discuss the imaging techniques currently available to visualize the glymphatic system as well as the automated methods currently available to measure PVS, and the strengths and limitations associated with each technique.

Evidence Level: 1
Technical Efficacy: Stage 1
utilizing two-photon laser scanning microscopy. By injecting a large-molecular weight tracer FITC-d2000 and a lower-molecular-weight tracer TR-d3 into the cisterna magna of mice they identified the pathway of CSF movement from the subarachnoid space, finding brain interstitial fluid was cleared via PVS. Additionally, they found small solutes were able to move from PVS into the brain parenchyma by bulk flow, whereas larger molecules were prevented by astrocytic end feet and remained in PVS to be glymphatically cleared from the brain. This method, however, was invasive and not a practical approach for assessing the glymphatic system in humans. Fluorescence microscopy causes photo-bleaching and damage in live tissue cells making it not applicable in live human tissue. Thus, the use of MRI was proposed.

Iliff et al then went on to assess the utility of contrast-enhanced T1w FLASH MRI sequences to image the glymphatic system in rats. This study assessed the exchange of CSF in the PVS using two different paramagnetic contrast agents Magnevist (gadopentetate dimeglumine, Gd-DTPA) and GadoSpin P (high-molecular-weight polymetric gadolinium-based contrast agent). It confirmed the pathway of the CSF from subarachnoid spaces through PVS into the brain tissue. They concluded that contrast-enhanced MRI was able to visualize the glymphatic pathway in rats and allowed visualization of the tracer throughout the entire brain volume. This can be beneficial for the identification of key areas of CSF influx into the PVS. The route of entry through the cisterna magna is not used in humans due to the risk of medullary injury. However, contrast-enhanced MRI using intrathecal injections can instead be used to visualize the glymphatic system. The intrathecal route is highly invasive and can be associated with significant adverse effects including infection, allergic reaction and spinal cord or nerve

![Figure 1](image1.png)

**FIGURE 1:** The perivascular unit. Source: Adapted from reference 1. Perivascular spaces (PVS) are potential cerebrospinal fluid (CSF) spaces shaped as a cylinder that surround the brain’s vasculature as it penetrates the brain. Astrocytes are glial cells whose end feet surround the arteries on the other side of the perivascular space and play a role in adjusting blood flow. Aquaporin-4 (AQP4) water channels are embedded in the astrocytic endfeet and facilitate the exchange of fluids.1,2

![Figure 2](image2.png)

**FIGURE 2:** Pathway through the glymphatic system. Source: (a) Taken from reference 6. Source: (b) Taken from reference 7. (a) Schematic of the pathway of CSF fluid through the glymphatic drainage system via perivascular spaces is shown. CSF enters the perivascular space surrounding the artery. The fluid then moves into the brain parenchyma via the AQP4 water channels. CSF enters the perivascular space surrounding veins, bringing any toxic proteins and metabolites (orange starburst shapes) from the brain tissue with it. Fluids, toxic proteins, and metabolites then drain through the glymphatic system, eventually draining into lymph nodes in the neck. (b) Green represents the lymphatic drainage from the brain into the cervical lymph nodes in the neck. Fluid drains from the ISF-meningeal connections along the dural venous system to the deep lymph nodes in the neck. CSF = cerebrospinal fluid; AQP4 = aquaporin-4; ISF = interstitial fluid.
injury.  

Additionally, the >2 hours scan time restricts accessibility of this technique for patients in routine clinical practice. Despite these limitations, contrast-enhanced MR cisternography is currently used in clinical practice to visualize and diagnose CSF leaks due to the higher sensitivity and specificity when compared to other imaging techniques. Thus, this method could be altered to visualize the flow of fluids through the glymphatic system in humans. In a cohort of healthy older adults, Zhou et al demonstrated the involvement of putative meningeal lymphatic vessels in the glymphatic pathway and validated the use of gadodiamide contrast-enhanced T1w and FLAIR MRI scans at multiple timepoints to visualize glymphatic clearance. Ringstad et al studied the use of gadobutrol as a contrast agent to visualize the glymphatic pathway over a period of 4 weeks (Fig. 3). They used standardized T1w MRI scans performed before contrast injection and at time points following the injection including at 24 hours, 48 hours, and 4 weeks in a cohort of healthy individuals and a cohort of patients with idiopathic normal pressure hydrocephalus (iNPH). They found the contrast-enhanced MRI could readily visualize the clearance of gadobutrol via the glymphatic system and delayed clearance in the iNPH cohort. Attempts to use the less-invasive intravenous (IV) route, rather than intrathecal, have also been made. Naganawa, Ohashi et al used the IV administration of gadolinium-based agents to visualize the enhancement of PVS 4 hours after injection on T2w FLAIR MRI scans. They found this technique was successful at identifying PVS in a cohort of healthy individuals, and a cohort of patients with endolymphatic hydrops. Gadolinium contrast is widely used for contrast-enhanced neuroimaging in clinical practice but can be associated with a rare but life-threatening allergy and is contraindicated in renal impairment. Newer approaches utilizing endogenous contrast techniques may be superior to exogenous contrast such as gadolinium. IV contrast-enhanced MRI offers the ability to dynamically visualize the flow of a tracer through the glymphatic system, which would be beneficial to better evaluate its function. Currently, other modalities only offer the visualization of the glymphatic system at stationary timepoints. However, this technique requires an intravenous infusion and scan at baseline, and then a scan 4 hours after the infusion to visualize the tracer in the PVS. Thus, it is time-consuming and may limit its translatability to clinical practice.

An alternative method for imaging the glymphatic system is diffusion tensor image analysis along the perivascular

![FIGURE 3: Imaging the glymphatic system by contrast-enhanced MRI. Source: Taken from reference 13. The glymphatic system was visualized in patients with idiopathic normal pressure hydrocephalus (iPH). Gadobutrol was used as the MRI contrast agent to visualize the CSF. Standardized T1w MRI scans were performed before and after intrathecal gadobutrol infusion at defined time points. Red represents areas of increased tracer uptake, green represents areas of moderate tracer uptake, and blue represents areas of poor tracer uptake. Scans taken from eight participants with iPH are shown. The color scale shows the percentage change in signal unit ratio. This demonstrates the clearance of the tracer in areas adjacent to the vasculature, most likely via PVS.](image_url)
space (DTI-ALPS). DTI-ALPS evaluates the diffusion capacity of water along PVS at areas of the brain where PVS and large white matter fibers are perpendicular. This is only possible where the medullary arteries and veins intersect with the ventricular wall. The ALPS index is the ratio of the diffusion capacity along the PVS on the outer side of the lateral ventricle to the diffusion capacity along the PVS running perpendicular to the main white matter fibers. The ALPS index scores are used to assess the flow of fluid through the glymphatic pathway.\textsuperscript{25,26} This method is noninvasive and has shorter scanning times, especially when compared to intravenous contrast MRI. However, there are disadvantages associated with DTI. First, it requires high-quality data and co-registration of susceptibility-weighted imaging (SWI) and DTI images. SWI is required to accurately identify the medullary vein structures, which PVS run concentrically to. DTI is unable to identify these structures and thus, co-registration is necessary to calculate the DTI-ALPS index. This registration is less accurate on highly atrophied brains such as those found in aged brains.\textsuperscript{27} Presently, DTI-ALPS can only measure the PVS in one region of interest, which does not provide information of the glymphatic system throughout the entire brain. It has been shown that poor glymphatic function in different areas of the brain may have different implications for disease.\textsuperscript{28–30} Overall, DTI-ALPS technique is relatively new and holds promise as a potential marker for glymphatic function. However, DTI-ALPS is only applicable in brain regions where the blood vessels are perpendicular to white matter; therefore, a whole-brain imaging technique would be favorable, and more research is required to validate its use in clinical practice.

**Enlarged PVS as a Marker of Poor Glymphatic Function**

As MRI technology has advanced, PVS have become more easily recognizable on MRI scans. They appear visible without contrast enhancement and can be easily identified on common sequences taken in clinical practice (Figure 4). Neurological diseases often warrant a brain MRI as part of their clinical work-up, therefore they are accessible in a clinical setting. PVS, as discussed earlier, are an important part of the pathway of the glymphatic system. PVS have been reported to become enlarged secondary to poor glymphatic elimination of obstructed waste products and removal of interstitial fluids.\textsuperscript{32–34} Typically, PVS are not seen on nonpathological structural MRI scans, and it is thought that they only become visible once they have become enlarged and glymphatic flow is reduced.\textsuperscript{31,35,36} Thus, enlarged PVS visualized on MRI may be a surrogate marker for poor glymphatic function.\textsuperscript{37}

**PVS in Disease**

**PVS in Neurodegenerative Diseases**

Numerous neurodegenerative diseases are proteinopathies, whereby the disease is associated with accumulation of one or more toxic proteins within the brain. One mechanism for accumulation of these proteins may be via reduced glymphatic clearance. Kress et al evaluated the glymphatic clearance of tracers in aged mice. They found that there was impaired drainage of the glymphatic system in aging brains.\textsuperscript{38} Since neurodegenerative diseases develop most commonly in older populations,\textsuperscript{39} it is possible that reduced glymphatic clearance of waste products predisposes the aging brain to the development of neurodegenerative disease. Glymphatic clearance has been demonstrated for many of the proteins implicated in neurodegenerative disease pathogenesis, such as tau and amyloid-beta.\textsuperscript{4,5,40–43}

As stated earlier, enlarged PVS can be used as a biomarker for poor glymphatic function. PVS have been found to be enlarged in patients with multiple sclerosis (MS) when compared to age- and sex-matched healthy controls.\textsuperscript{44–48} Wuerfel et al measured PVS volumes on T1w, T2w and FLAIR MRI scans. They quantified higher volumes of PVS in the MS cohort when compared to the controls. Additionally, within the MS cohort, there was no significant association between the volume of PVS and the brain parenchymal fraction ($P = 0.126$) implying the degree of brain atrophy had no effect on the PVS measurements. Conforti et al also found higher PVS number and volume in MS patients ($n = 40$) compared to healthy controls ($n = 30$) independent of the degree of global cortical atrophy measured by the brain parenchymal fraction ($P = 0.41$).\textsuperscript{46} Thus, it was concluded that the volume of PVS was greater in the MS cohort independent of the degree of brain atrophy.\textsuperscript{45,46} Wuerfel et al also performed a longitudinal sub-study on 18 patients who had MRIs available at baseline and at 12 months. They found in scans with contrast-enhancing lesions (CEL), there was a significant increase in PVS number and volume from the preceding scan without the presence of CEL ($P = 0.011$). Additionally, PVS volumes were lower when CEL were absent when compared to a preceding scan where the CEL was present ($P = 0.085$).\textsuperscript{45} This demonstrates that enlarged PVS may be used as a dynamic marker for disease activity for patients with MS.\textsuperscript{45,47}

The inflammatory response in MS is thought to cause PVS enlargement due to the infiltration of inflammatory cells and fluid into the PVS. This could be due to either increased demyelinating disease activity or the breakdown of the blood–brain barrier during the inflammatory response.\textsuperscript{46}

Studies have also shown an enlargement of PVS in patients with Parkinson’s disease (PD).\textsuperscript{49,50} Shen et al found increased PVS volumes ($P = 0.015$) and numbers ($P = 0.035$) in the basal ganglia for patients with early-onset PD ($n = 40$) when compared with healthy controls ($n = 41$).\textsuperscript{49} Additionally, they found that there was a significant positive association between the PVS count in the basal ganglia and the disease severity ($P = 0.005$) measured by the Movement Disorder Society-sponsored revision of the Unified Parkinson’s Disease Rating Scale (MDS-UPDRS).\textsuperscript{49} Thus, there is potential for PVS to be used as a marker for...
disease severity in PD. One of the pathological hallmarks of PD is the presence of Lewy bodies. Lewy bodies are created by the abnormal aggregation of α-synuclein protein. $\alpha$-synuclein proteins have been shown to be cleared from the brain via the glymphatic system. However, it is currently uncertain whether the poor glymphatic drainage of $\alpha$-synuclein protein increases its deposition and formation of Lewy bodies, or whether the damage of neurons releases $\alpha$-synuclein protein, which accumulates in PVS and prevents normal glymphatic clearance.

Alzheimer’s disease (AD) involves two major pathological hallmarks—1) the formation of extracellular amyloid-beta (Aβ) plaques and 2) the formation of neurofibrillary tangles due to intracellular accumulations of hyperphosphorylated tau proteins. Both of these proteins have been found to be cleared from the brain via PVS. Studies have shown larger PVS in patients with AD when compared with healthy controls. PVS have been thought to become enlarged secondary to deficiencies in clearance of amyloid and tau proteins. Hansen et al found a significantly higher burden of PVS measured on T1w MRI scans for patients with AD, and that their quantitative PVS burden scores were able to discriminate patients with AD from age-matched healthy controls ($P < 0.001$). Boespflug et al found larger numbers of enlarged PVS in postmortem samples of patients with AD when compared with postmortem samples from healthy controls ($P < 0.01$). Additionally, they found an increased PVS burden was associated with the presence of Aβ and tau pathology demonstrating a potential causal link between poor glymphatic clearance and abnormal aggregation of these proteins. There is some evidence to suggest that enlarged PVS could be used to differentiate patients with mild cognitive impairment (MCI) from cognitively healthy controls. Niazi et al found dilated PVS had a sensitivity of 92.86% and specificity of 93.33% for this distinction. However, PVS have found to be enlarged in a range of different neurodegenerative diseases and therefore is unlikely to be highly specific to MCI. For example, PVS have been shown to be enlarged in other forms of dementia, such as vascular dementia and frontotemporal dementia when compared to healthy controls. Overall, PVS is likely to play an integral role in the development of a range of proteinopathies.

**PVS in Other Diseases**

PVS have also been found to be enlarged in other brain diseases, implicating that the glymphatic system dysfunction may contribute to a wide variety of pathologies. There have been multiple reports of enlarged PVS in pediatric populations of idiopathic generalized epilepsy. Liu et al found that in children with newly diagnosed idiopathic...
generalized epilepsy, there were higher PVS number and volumes compared with healthy controls. Additionally, they found a positive correlation between the seizure duration and the PVS burden and that after the seizure onset, the PVS burden gradually decreased with time.\textsuperscript{66} This could be explained by the release of tau protein in response to axonal injury caused by the seizure.\textsuperscript{68,69} Thus, an accumulation of tau in the brain could cause an enlargement of the PVS and poor drainage via the glymphatic system.

Imaging of the glymphatic system has shown that drainage is impaired after a mild traumatic brain injury (TBI).\textsuperscript{70,71} Li et al found that in rats with mild TBI, the suppression of normal glymphatic drainage indicated a persistent injury of the brain.\textsuperscript{70} Additionally, Koo et al found that a high burden of PVS in the centrum semi-ovale detected by MRI indicated a greater chance of developing subdural fluid.\textsuperscript{72} This is likely due to the poor glymphatic function leaving the brain susceptible to the accumulation of toxic proteins and metabolites, causing further neuronal damage after the initial traumatic event.

The glymphatic drainage has also been studied in idiopathic normal pressure hydrocephalus. Studies have found delayed clearance of tracers via the glymphatic system in these patients.\textsuperscript{13,25,73,74} Therefore, poor glymphatic drainage may contribute to the development of the disease. PVS may be a useful marker for the glymphatic function and could potentially aid in diagnosis of these patients on imaging. However, to date, no studies have measured PVS in a cohort of patients with idiopathic normal pressure hydrocephalus.

Barisano et al studied PVS in a cohort of astronauts from NASA and the European Space Agency, and cosmonauts from Roscosmos. They measured the PVS burden for these participants prior to their mission, and after their 6-month residency on the International Space Station. They found increased PVS burden in both the basal ganglia and white matter (WM) after their spaceflight. Additionally, those who developed spaceflight associated neuro-ocular syndrome (SANS) had larger WM PVS volumes pre- and post-spaceflight when compared to astronauts who did not develop SANS.\textsuperscript{75}

Overall, PVS have been implicated in a wide range of diseases. Accurate methods for PVS detection are required to further investigate the role of the glymphatic system in disease pathogenesis and progression.

Visual Rating Scales to Measure PVS

The initial studies investigating PVS burden counted the number of PVS observed on MRI. This remains the gold standard for assessing PVS burden, however, it is very time consuming. Subsequently, numerous visual rating scales have been developed to simplify and standardize the measurement of PVS.\textsuperscript{31,58,60,76–78} The most widely utilized is Wardlaw et al’s STRIVE criteria.\textsuperscript{31} This criterion involves manually counting PVS on selected slices from the centrum semi-ovale, basal ganglia, and midbrain on brain MRI scans. Using these manual counts, the scan is then assigned a category on Wardlaw’s PVS scale to quantify the PVS burden (Fig. 5).\textsuperscript{76}

There are many limitations associated with visually evaluating PVS, described in Table 1. Automated quantification allows for more accurate measurement of enlarged PVS and may allow the use of PVS as a biomarker for disease progression.

Automated Programs to Measure PVS

Numerous automated algorithms have been developed to improve the reliability of PVS measurement and its utility as a biomarker for the glymphatic system.\textsuperscript{53,59,80–83,85–91} The development of these algorithms allowed for both the number of PVS (as is measured using visual rating scales) as well as the PVS volume to be calculated. Both these measurements have been interchangeably used as markers of PVS burden in the literature.\textsuperscript{53,59,80–83,85–91} Multiple techniques have been attempted to develop an algorithm that is accurate and clinically applicable (Table 2, Fig. 6). These algorithms can be broadly categorized into intensity-based thresholding approaches, which apply an intensity threshold to find PVS, vesselness-filter approaches, which apply a filter to enhance tubular structures, and machine learning approaches, which learn patterns in labeled images indicative of PVS.

Intensity-Based Thresholding Approaches

Ramirez et al used the “Lesion Explorer” program, originally designed to exclude PVS from its analysis, to instead identify PVS using intensity thresholds.\textsuperscript{32} This program requires manual input of thresholds, which can be subjective and may differ depending on both the investigator and the quality of the individual scans.\textsuperscript{91} Wang et al also used a semi-automated program to measure the volume and number of PVS. They found a large variance for the intensity levels of PVS on T2w images within their dataset, so they adjusted their intensity thresholds in three stages. First, normalization to change the range of intensity values utilized, then they applied a gamma correction factor of 2, and finally they used linear mapping to follow the PVS along its entire length between each axial slice.\textsuperscript{83} Niazi et al and Cai et al utilized edge detection and k-means clustering to segment PVS.\textsuperscript{55,59} In these studies, the requirement for a manual choice of parameters or editing of masks can be time consuming and may introduce inter-observer variability between investigators and studies. Ramirez et al and Wang et al used images from a 1.5 T scanner and 2D methods, which means the program may not be optimized for 3 T images that are more sensitive to detecting PVS.\textsuperscript{32,83} Analysis of PVS in a 3D computational algorithm, such as that proposed by Niazi et al\textsuperscript{59} and Cai et al,\textsuperscript{55} rather than Ramirez et al\textsuperscript{32} and Wang et al,\textsuperscript{83} would be more useful in detecting PVS which often travel in varying directions.
Fully automated algorithms have been developed to reduce the need for manual inputs such as the Multimodal Autoindentification of Perivascular Spaces (MAPS) created by Boespflug et al.\cite{88} MAPS identifies PVS using features including their relative intensity to surrounding voxels, cluster size, and degree of linearity. MAPS is beneficial in showcasing the distribution of PVS in a 3D manner and therefore has a greater ability to detect more subtle changes in PVS longitudinally. One limitation of this algorithm, however, is the need for manual input to visually confirm successful co-registration to ensure there are no omissions of PVS during the white matter extraction. Additionally, the original program required four volumetric sequences (T1w, T2w, FLAIR, and proton density MRI scans) for the program to run.\cite{88} In clinical practice, often only one volumetric sequence is obtained. Although multiple volumetric sequences can improve the certainty of identifying PVS, it also introduces more artifacts into the image as the patient has to spend more time in the scanner.\cite{94} Subsequent modifications to the algorithm to use fewer sequences (T1w and FLAIR MRI scans only) have demonstrated promising results with a positive predictive value of 77.5% in a cohort of older dementia-free adults (aged 70–101 years) and 87.5% in a different cohort of older adults (aged 58–92 years), indicating a high true positive rate for detecting PVS.\cite{81} This algorithm, however, currently can only be used to assess PVS in white matter as it relies strongly on local intensity contrast, which is lower in other areas of the brain. Since PVS have been found to be significant in other areas of the brain, particularly the basal ganglia and midbrain,\cite{95,96} it would be useful to develop a program that can measure the PVS burden in these regions as well.

**Vesselness Filter Approaches**

There have been numerous automated programs created utilizing the Frangi filter\cite{97} to detect PVS based on vesselness rather than on linearity.\cite{82,86,89} The Frangi filter utilizes a hessian matrix to find the principal directions of the second-order structures in the image.\cite{97} This can be used to identify the long tubular structures and has been shown to increase the specificity of identifying PVS.\cite{89} Ballerini et al utilized ordered logit models to evaluate what parameters are required from the Frangi filter to obtain the greatest likelihood that a structure is a PVS in the centrum semiovale.\cite{89} The program showed a high concordance with visual rating scores ($r = 0.75$). sepehrband et al improved detection of PVS by enhancing the intensity profiles during the postprocessing step termed “enhanced PVS contrast” (EPC), by combining T1- and T2-weighted images. Their results showed that their EPC enabled greater detection of PVS compared to using a
Their program also required multiple volumetric sequences, improving the accuracy but making clinical translation challenging. There was significant variance when comparing the automatic program on different imaging modalities within the study data. The number of PVS quantified varied significantly depending on the MRI sequence utilized \((P = 6.3 \times 10^{-19})\). Thus, the program must be applied to the same imaging modality across the dataset. Additionally, the automated program requires T1w and T2w scans to be taken at the same resolution. This limits its use in clinical practice, as these scans are often acquired at different axial slice thicknesses.

**Combination of Vesselness and Intensity Approaches**

Spijkerman et al used a combination of intensity and vesselness parameters to identify PVS and measure the number of PVS in a single slice. They applied their method to a dataset of healthy individuals aged 27–78 years with 7 T MRI scans available. They achieved a dice score of 0.61 and a count correlation of 0.76. Although, Spijkerman et al were only able to measure PVS counts in a 2D slice, which could be useful for comparisons with manual rating scores. However, this approach does not provide an assessment of the PVS burden for the entire brain volume. Additionally, greater similarity to the ground-truth (measured by the dice score) have been achieved by utilizing machine learning approaches.

**Machine Learning Approaches**

Numerous machine learning approaches have been used to measure PVS burden. Park et al used a random forest model with randomized 3D Haar features to extract the tubular structures of PVS. This learning-based model has the advantage of not requiring manual input to set...
### TABLE 2. Automated Programs and Their Associated Advantages and Limitations

#### Intensity-Based Thresholding Approaches

| References       | Method                                                                 | Modalities | Advantages                                           | Limitations                                                                 |
|------------------|------------------------------------------------------------------------|------------|------------------------------------------------------|----------------------------------------------------------------------------|
| Ramirez et al    | The “Lesion Explorer” program, originally designed to exclude PVS from its analysis, to instead identify PVS using intensity thresholds | • T2w      | • Minimal manual interventions per scan              | • Only measured PVS in a 2D manner                                         |
|                  |                                                                        | • PD       | • Good interrater reliability                        | • Semiautomatic approach                                                   |
|                  |                                                                        |            |                                                     | • Measured on 1.5 T scanner                                                |
| Wang et al       | Gamma correction and linear mapping                                     | • T2w      | • Able to use on low-resolution scans with thick axial slices and significant background noise | • Only measured PVS in a 2D manner                                         |
|                  |                                                                        |            |                                                     | • Semiautomatic approach                                                   |
|                  |                                                                        |            |                                                     | • Measured on 1.5 T scanner                                                |
|                  |                                                                        |            |                                                     | • Only measured PVS in basal ganglia                                       |
| Cai et al        | Edge detection and k-means clustering                                    | • T2w      | • Identifies PVS distribution in a 3D manner         | • Semiautomatic approach                                                   |
| and Niazi et al  |                                                                        |            |                                                     | • Requires consistent imaging set-up                                       |
|                  |                                                                        |            |                                                     | • Only measured PVS in centrum semiovale                                   |
| Boesplfug et al  | MAPS that assesses the relative intensity of neighboring voxels and then uses a linearity model to identify PVS | • T1w      | • Fully automated                                   | • Multiple imaging modalities required to run                              |
| and Schwartz et al |                                                                     | • T2w      | • Identifies PVS distribution in a 3D manner         | • Manual input required to confirm successful co-registration visually     |
|                  |                                                                        | • FLAIR    |                                                     | • Can only be used on centrum semiovale                                    |
|                  |                                                                        | • PD       |                                                     |                                                                             |

#### Vesselness Filter Approaches

| References       | Method                                                                 | Modalities | Advantages                                           | Limitations                                                                 |
|------------------|------------------------------------------------------------------------|------------|------------------------------------------------------|----------------------------------------------------------------------------|
| Sepehrband et al| Enhanced contrast then Frangi filter to identify PVS based on “vesselness” | • T1w      | • Fully automated                                   | • Multiple imaging modalities required to run                              |
|                  |                                                                        | • T2w      | • Enhanced contrast allows better visual and automated detection of PVS | • Can only be applied to data sets using the same imaging modalities       |
|                  |                                                                        | • PD       |                                                     |                                                                             |
| Ballerini et al  | Ordered logit models then Frangi filter to identify PVS based on “vesselness” | • T1w     | • Fully automated                                   | • Multiple imaging modalities required to run                              |
|                  |                                                                        | • T2w      | • High concordance with visual rating scales         |                                                                             |
|                  |                                                                        | • PD       |                                                     |                                                                             |

#### Combination of Intensity and Vesselness Approaches

| References       | Method                                                                 | Modalities | Advantages                                           | Limitations                                                                 |
|------------------|------------------------------------------------------------------------|------------|------------------------------------------------------|----------------------------------------------------------------------------|
| Spijkerman et al |                                                                        | • T1w      | • Good reproducibility                               | • Only measures PVS in a 2D manner                                         |
|                  |                                                                        | • T2w      |                                                     |                                                                             |
the intensity thresholds thus improving the segmentation accuracy. This also allows the program to be used on different datasets scanned by different machines. Park et al tested their method against intensity thresholding, vesselness thresholding and learning-based methods using the conventional Haar features. They found that their method most resembled the ground-truth in respect to distribution and detection of true PVS. Their study analyzed high-resolution MR images from healthy young individuals who have lower PVS burden than aged populations. Therefore, it is hard to ascertain whether this trained algorithm would generalize to older populations with a much greater number of PVS. Zhang et al used a structured random forest model with vascularity filters to differentiate the PVS from its background with an entropy-

| References | Method | Modalities | Advantages | Limitations |
|------------|--------|------------|------------|-------------|
| Park et al11 | Machine learning using a random forest model with randomized 3D Haar features | T1w, T2w | • Does not require manual inputs to set intensity thresholds • Can be used on different datasets scanned by different machines | • Young, healthy patients (25–37 years) • Measured on 7 T scanner |
| Hou et al. 90 | Machine learning using a Convolutional Autoencoder and a U-Shaped Neural Network | T1w | • No manual input of thresholds • Can be used on different datasets taken from different scanners | • Requires a large number of manual segmentations for validation • Poor performance in white matter • Young, healthy patients (18–35 years) |
| Boutinaud et al92 | Machine learning using a convolutional neural network regression model | T2w | • Trained using a different network for different regions to improve PVS detection in different areas of the brain | • Measured on 1.5 T scanner • Only able to be used on scans acquired from the same scanner |
| Dubost et al. 80 | Machine learning using a fully convolutional neural network | T2w | • No manual input of thresholds • Can be used on different datasets taken from different scanners | • Young, healthy patients (25–55 years) • Measured on 1.5 T scanner |
| Lian et al13 | Machine learning using a convolutional neural network | T2w | • | • |

MRI = magnetic resonance imaging; T1w = T1 weighted; T2w = T2 weighted; PD = proton density; FLAIR = fluid-attenuated inversion recovery; T = tesla.
based sampling to train their model. This achieved a similar performance (dice score of 0.66) to the random forest model with randomized 3D Haar features described by Park et al. (dice score of 0.64). Hou et al. describe a method of enhancing MR images to better identify and analyze PVS prior to using the previous algorithm created by Park et al. Their enhanced and denoised images produced the best results for PVS segmentation. There were, however, errors at the border of white matter and gray matter where the thin edges appeared similar to the structures of PVS. Additionally, they had a small study cohort of 17 MRI scans affecting the parameters used for intensity ranges. Moreover, due to the extremely high resolution of the images, scans may pick up nonenlarged PVS and deep medullary veins. Deep medullary veins can be mistaken for PVS by these programs due to their similar intensities and therefore would require manual observer correction. These studies utilized 7 T MR imaging, which is a useful tool in research as it produces extremely high-resolution images. However, 7 T is rarely used clinically, so the clinical translation of research at 7 T is limited at the present time.

A machine learning approach using an autoencoder and U-shaped network was created by Boutinaud et al. They applied their algorithm on a dataset of T1w MRIs taken from a 3 T scanner of healthy young adults. This method had an average performance producing a dice score of 0.64. However, an advantage was this method was able to be used on different datasets taken from different scanners. Another machine learning approach is the use of a convolutional neural network to identify PVS. Dubost et al used a convolutional neural network regression method to quantify PVS in the basal ganglia in T2w MRI scans acquired on a 1.5 T scanner. They found a high intraclass correlation coefficient between the visual scores and automated scores. Lian et al. used a fully convolutional neural network (FCNN) machine learning approach on a dataset of T2w MRIs acquired on a 7 T scanner. Their FCNN approach had no requirement for manual inputs to measure PVS in a cohort of healthy subjects aged from 25 to 55 years. They compared their results to other available methods for PVS segmentation including using the Frangi vesselness filter, structured random forest machine learning approach and a U-net machine learning approach. They found that their method was superior (dice score of 0.77 using the FCNN compared to 0.53 using the Frangi filter, 0.67 using the structured forest approach and 0.72 U-net approach). An advantage of this algorithm was that it was able to detect PVS in the entire brain volume. Although, it did detect some false positives around the ventricles. Lian et al propose that using a reliable white matter mask could reduce the number of false positives, but this comes at the cost of only detecting the PVS burden in part of the brain. Additionally, this method could not detect

FIGURE 6: Automated PVS detection methods. The three main techniques for automated PVS segmentation are shown with their associated literature: intensity thresholding, vesselness filter, and machine learning. (a) The final PVS mask created from the lesion explorer program using intensity-based thresholds to identify PVS. (b) The final PVS mask created using enhanced PVS contrast and the Frangi filter to identify PVS based off vesselness. (c) The ground truth PVS mask. (d) The final PVS mask created using the Haar transform of nonlocal cubes and block-matching filtering. (e) The 3D rendering of the ground truth PVS mask. (f) The 3D rendering of the final PVS mask using the Haar transform of nonlocal cubes and block-matching filtering machine learning technique.
PVS where the difference in contrast between the PVS and the surrounding tissue was low. Their FCNN may not be applicable to scan resolutions typically seen in clinical practice, which have poorer contrast to noise ratios. Thus, there is still a need for a clinically applicable automated method for measuring PVS.

Conclusion

There is increasing evidence that PVS are a marker of reduced glymphatic flow and may be a useful biomarker in a large range of diseases. Efforts have been made to image the glymphatic system using two-photon laser microscopy, contrast-enhanced MRI and diffusion tensor imaging. PVS can be visualized on standard MRI sequences when enlarged and may be a useful biomarker for glymphatic function. Application of various image processing methodologies to the identification of PVS on MRI is enabling automatic detection of PVS negating the need for manual counting of PVS. To date, automated algorithms have been tested in young healthy populations and are limited by the need for multiple volumetric sequences or imaging at 7 T, neither of which are common in routine clinical practice. Future studies should focus on validating these algorithms for use on routine clinical imaging data, such as volumetric T1w MRIs taken on 3 T scanners, and in disease populations.

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