Effect of Intensity Standardization on Deep Learning for WML Segmentation in Multicentre FLAIR MRI

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Abstract

Deep learning methods for WML segmentation in MRI suffer a reduction in performance when applied on data from a scanner or center that is out-of-distribution (OOD) from the training data. This is critical for translation and wide scale adoption, since current models cannot be readily applied to data from new institutions. In this work, we evaluate several intensity standardization methods for MRI as a preprocessing step for WML segmentation in multicentre FLAIR MRI. SC-UNet was trained on the standardized images, as well as the original data and segmentation performance was evaluated over several dimensions. The training (in-distribution) data consists of a single study, of 60 volumes, and the test data is 128 unseen volumes from multiple clinical datasets (OOD). Results show the proposed IAMLAB and Ensemble provide higher WML segmentation performance compared to models from original data or other normalization methods. IAMLAB & Ensemble have the highest DSC on the in-distribution data (0.78 & 0.80) versus 0.75 in the original data. More importantly, on clinical OOD data, DSC was highest for IAMLAB compared to the original data for all lesion categories (LL>25mL: 0.77 vs. 0.71; 10mL≤ LL<25mL: 0.66 vs. 0.61; LL<10mL: 0.53 vs. 0.52). The performance increase compared to the original data was shown through t-tests to be statistically significant. All this taken together indicates that IAMLAB and Ensemble normalization methods are mitigating MRI domain shift and are optimal for WML segmentation in unseen FLAIR MRI datasets.

Keywords: Standardization, deep learning, WML, segmentation, FLAIR MRI

1. Introduction

White matter lesions (WML), or leukoaraiosis, are routinely found in the aging brain and are established cerebral vascular disease (CVD) markers (Wardlaw et al., 2015)(Pantoni, 2010)(Azizyan et al., 2011). WML represent increased and altered water content in hydrophobic white matter fibers and tracts. Changes in white matter vasculature likely contributes to WML pathogenesis (Gorelick et al., 2011). WML may be the result of ischemic injury from decreases in regional cerebral blood flow (Pantoni and Garcia, 1997). Demyelination and axonal degeneration have also been suggested as probable mechanisms (Wardlaw et al., 2015). Typically, WML manifest as multifocal, diffuse periventricular or subcortical lesions of varying morphologies (Marek et al., 2018). The presence of WML is associated with cognitive decline, dementia, stroke, death, and lesion progression increases these risks (Debette and Markus, 2010)(Alber et al., 2019). Therefore, WML are significant clinical biomarkers for investigation.

In T2-weighted and fluid-attenuated inversion recovery (FLAIR) magnetic resonance images (MRI), WML appear as hyperintense signals in the cerebral white matter (Marek

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et al., 2018). FLAIR MRI is preferred for WML analysis (Azizyan et al., 2011), (Badji and Westman, 2020), (Wardlaw et al., 2013), since the high signal from the cerebrospinal fluid (CSF) in T2 is suppressed, thus highlighting white matter disease (Lao et al., 2008). This is due to increased water content secondary to ischemia and demyelination and much more robustly seen in FLAIR than with T1/T2 (Gorelick et al., 2011). WML classification is typically performed by a radiologist using visual rating systems such as the Fazekas scale (Fazekas et al., 1993) or by manual segmentation (Caligiuri et al., 2015). Manual segmentation is time-consuming, laborious, and has high inter and intra-variability (Caligiuri et al., 2015). For objective, consistent, and efficient WML analysis, automated WML segmentation methods have been the focus of extensive research efforts in recent decades.

There have been many WML frameworks in the past for FLAIR MRI, that consider unsupervised methods (Caligiuri et al., 2015) (Khademi et al., 2011)(Khademi et al., 2014), supervised methods (Anbeek et al., 2004) (De Boer et al., 2009) (Simões et al., 2013) (Knight et al., 2018) (Schmidt, 2017) and deep learning methods more recently. Comparisons of WML algorithms, such as in (Heinen et al., 2019), have emerged evaluating the performance of five automated WML segmentation methods in a multicentre FLAIR and T1 dataset. The methods mainly consisted of traditional machine learning (ML) algorithms and performance is reported for 60 volumes from six centres. Using similar WML segmentation methods, in (de Sitter et al., 2017), the authors investigate five WML segmentation tools for multiple sclerosis (MS) lesion segmentation using FLAIR and T1 images for 70 patients from six centres. In (Vanderbecq et al., 2020), the authors considered seven open source traditional WML segmentation methods for T1 and FLAIR and studied performance on research and clinical datasets. In (Frey et al., 2019), the authors provide a meta-review of the current WML segmentation methods applied in large-scale MRI studies.

One of the key limitations in machine learning models is poor testing performance on out of distribution (OOD) data - data that is not within the training distribution (In Distribution, ID). This is especially true for MRI, as variations in hardware and software create non-standard intensities, contrasts, and noise distributions across scanners. As shown in (Khademi et al., 2021), CNN algorithms typically perform the best for WML segmentation, but do not equally generalize across scanners and datasets. This domain gap is a significant problem for deployment and limits wide scale adoption, since models will not work equally well in new centres. One method to reduce the domain gap is intensity standardization (Reiche et al., 2019). Intensity standardization is the process of aligning the intensity histogram to some known distribution which maps the same tissues to the same intensity ranges. In this work, we evaluate several intensity normalization methods for FLAIR MRI, for WML segmentation performance OOD data.

2. Methods and Materials

2.1. Data

Experimental data for this work comes from 4 multicentre FLAIR MRI datasets. Sixty volumes from the MICCAI WML Segmentation Challenge (Kuijf et al., 2019) are used to train the models (ID) and the remaining is used for held-out OOD testing. The three OOD clinical datasets are from the Alzheimer's disease Neuroimaging Initiative (ADNI) (Aisen et al., 2015), the Canadian Atherosclerosis Imaging Network (CAIN) (Tardif et al.,

Table 1: FLAIR MRI ground truth datasets. All data is 3T and 3-5mm slice thickness.

	Patient Information					
Database	**Disease**	**Volumes**	**Images**	**Patients**	**Centres**	**LL ± SD (mL)**
ADNI	Dementia	35	1225	35	22	11.8 ± 10.1
CAIN	Vascular	63	3024	63	8	12.2 ± 12.3
CCNA	Dementia	30	1440	30	7	22.8 ± 18.8
MICCAI	Vascular	60	3580	60	3	17.6 ± 17.4
Total	All	188	9.27K	188	39	15.0 ± 15.2

	Acquisition Parameters					
Database	**GE/Philips/Siemens**	**TR (ms)**	**TE (ms)**	**TI (ms)**	**X Spacing (mm)**	**Y Spacing (mm)**
ADNI	10/7/18	9000-11000	90-154	2250-2500	0.8594	0.8594
CAIN	12/35/16	9000-11000	117-150	2200-2800	0.4285-1	0.4285-1
CCNA	2/3/25	9000-9840	125-144	2250-2500	0.9375	0.9375
MICCAI	20/20/20	4800-11000	82-279	1650-2500	0.9583-1.2	0.9583-1.2
Total	44/65/79	4800-11000	82-279	1650-2800	0.4295-1.2	0.4295-1.2

2013), a pan-Canadian clinical study on vascular disease, and the Canadian Consortium on Neurodegeneration in Aging (CCNA), a pan-Canadian clinical study to analyze different types of dementia (Chertkow et al., 2019) (Mohaddes et al., 2018). Data from CAIN, ADNI, CCNA and MICCAI have pixel-wise WML annotations. See (Khademi et al., 2021) for the annotation protocol for CAIN, CCNA and ADNI. Table 1 shows the acquisition parameters.

2.2. Intensity Standardization

Intensity standardization is performed to remove variability caused by the multicentre effect using a modified version of our original work in (Reiche et al., 2019) called IAMLAB. The original work performs 3×3 median filter denoising, bias field correction through lowpass filtering, and intensity standardization. Intensity standardization is achieved through a novel scaling factor that aligns the histogram modes of two volumes. As shown in (Reiche et al., 2019), the intensity intervals of tissues in 350K FLAIR MRI are more consistent across multicentre data using this approach. Slice refinement was removed which improves robustness since peak detection failed in upper and lower slices (and reduced alignment performance) and N4 bias field correction was used. Our method is compared to several other methods in the literature, including Nyul (Nyul and Udupa, 1999), which provides piece-wise histogram matching, z-score normalization and White Stripe (Shinohara RT, 2014), which provides a z-score normalization within a specific percentile.

2.3. WML Segmentation

The skip connection (SC) U-Net proposed in (Wu et al., 2019) is used in this work as it was found to be optimal for FLAIR-only WML segmentation compared to UNet, Multiresnet and ResNet approaches (Khademi et al., 2021). SC UNet adds skip connections between the shallow and deep layers of a CNN architecture. The outputs from each max-pooling layer in the encoder arm are inputs for each transposed convolution layer in the decoder. Skip connections ease training through improved information and back-propagation flow (Wu et al., 2019), (Drozdzal et al., 2016) which has been shown to diminish vanishing gradients (Drozdzal et al., 2016). Generalized dice loss (Sudre et al., 2017), Adam Optimizer with a learning rate of 1e-4 over 100 epochs, and batch size of 64 were used. Images were patched into 64 x 64 regions with 50% overlap. Slight data augmentations were applied for rotation, scaling, shearing, scaling and translation (Li et al., 2018). Models were trained on a computer with a NVIDIA Tesla P100 GPU with 16GB of RAM.

2.4. Performance Metrics

The KL-divergence is used to measure alignment between the average volume histogram of the dataset and each individual volume histogram. A low KL divergence indicates high alignment in intensities across the dataset. The evaluation metrics used in the MICCAI WML segmentation competition were used which includes the dice similarity coefficient (DSC), the H95, average volume difference (AVD), F1-score and Recall (Kuijf et al., 2019). The extra fraction (EF) was also used to measure the relative false-positive rate. To determine whether segmentation performance is significantly improved using intensity standardized data, a t-test is conducted between performance metrics for predictions from standardized and original data. Box-cox transformation is used to normalize distributions (except for AVD). Stochastic neighbour embedded (t-SNE) graphs (Hinton and Roweis, 2003) are also investigated to examine patterns in the data. The t-SNE method uses a pre-trained CNN and a projection of the feature representations onto two dimensions. Features similar to one another are overlapping in the feature space. The t-SNE graphs for original and normalized data, across different scanners.

3. Results

The multicenter datasets listed in Table 1 are standardized using IAMLAB, white stripe, Nyul and z-score. SC-UNET was trained separately for the original data, IAMLAB, Whitestripe, Nyul and Z-score standardization methods for WML segmentation, resulting in five models in total. An Ensemble method is considered, which takes majority vote over all intensity standardization methods on a per-pixel basis. The entire MICCAI dataset (which is balanced between GE, Philips and Siemens) is used for training all the models, and the held-out (unseen) clinical data (CAIN, CCNA, ADNI) are used to examine generalization. Three folds are used (approximately 67% for training, and 33% to testing) for all experiments. Prior to intensity standardization and WML segmentation, skull-stripping is performed on the volumes using U-NET for intracranial volume (ICV) segmentation (DiGregorio et al., 2021).

3.1. Intensity Standardization

Histograms of original and standardized volumes for WML only for all datasets and images are shown in Figure 1. To quantify the degree of alignment to the mean intensity distribution for each method, the KL-distance was computed and is shown in Figure 1. IAMLAB normalization has the best alignment (lowest KL) of all the methods, with KL = 0.06, compared to the original data with KL = 0.83. For reference, the intensity normalized histograms for the entire brain and FLAIR MRI slices of original and standardized image are shown in Figure 5 and 6. The t-SNE results for the various standardized and original datasets are shown in Figure 7, which shows features from different scanner vendors are more overlapping in the standardized images. The original data has non-overlapping clusters for the different scanners, indicating different feature mappings.

3.2. WML Segmentation: In Distribution

First, the model is verified using only the MICCAI dataset. MICCAI was divided into training/testing sets and evaluated over three fold cross validation and all 60 volumes were

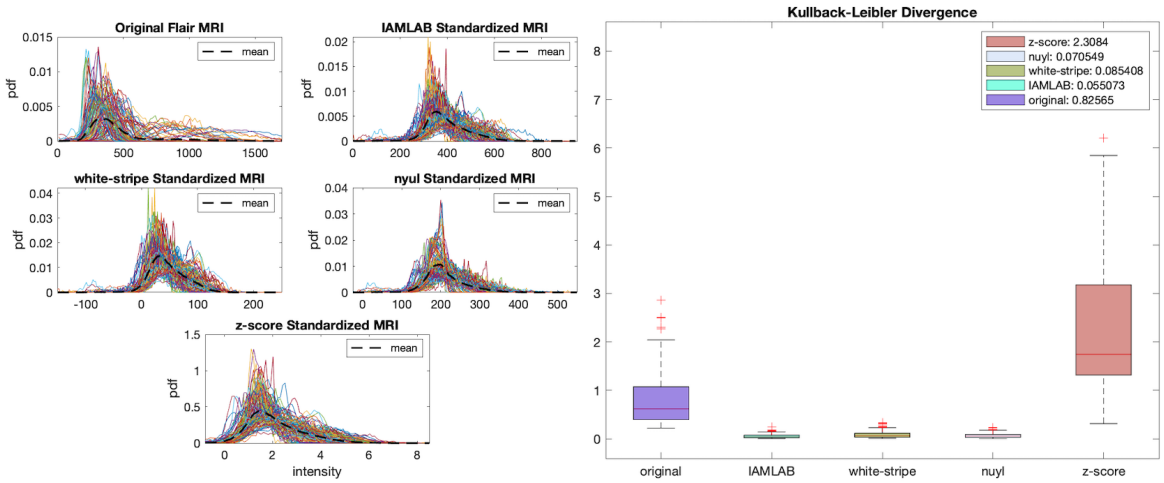

Figure 1: Left: WML histograms of ground truth data over all normalization methods. Right: KL divergence for all metrics on the ground truth data.

independently tested. Example segmentations are shown in Figure 2. As can be seen the model built on original data misses some of the WML, which are detected on the normalized data. Mean validation metrics are shown in Table 2 where bold means best DSC. IAMLAB (0.78) and Ensemble (0.80) had the highest DSCs (original DSC = 0.75), which are similar to the top ranked teams in the MICCAI competition. The Ensemble method had leading metrics in other categories, except for EF, which original was lowest and likely related to under-segmentation in Figure 2. Segmentation performance of top intensity standardized models (IAMLAB, Ensemble) were statistically different from the original data.

Table 2: Model validation: WML segmentation performance on 60 MICCAI.

	DSC	**EF**	**H95**	**AVD**	**F1-score**	**Recall**
Original	0.75	**0.14**	5.34	26.60	0.71	0.66
Nyul	0.76	0.16	5.32	22.47*	0.68	0.63
White-Strip	0.78*	0.17	5.25	19.72*	**0.72***	0.66
Z-Score	0.78*	0.17	4.78	20.01*	0.72*	0.69
IAMLAB	0.78*	0.18	4.59	20.08*	0.71	0.69
Ensemble	**0.80***	0.28	**4.52***	**19.46***	0.71	**0.78***

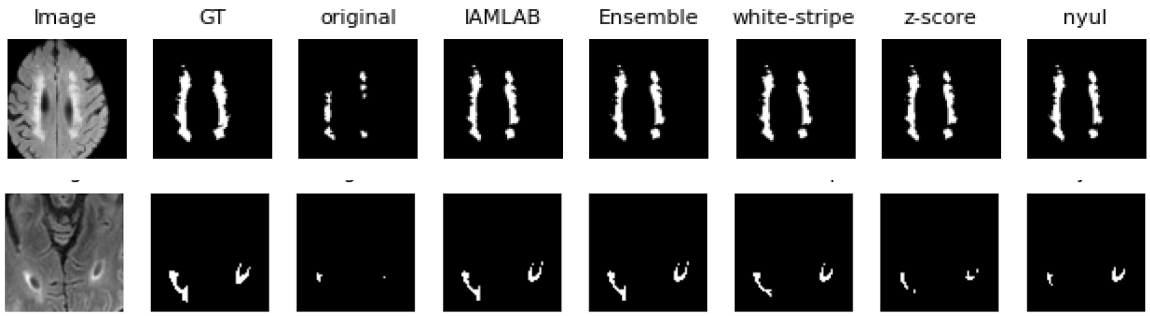

Figure 2: SC-UNET trained with MICCAI tested on MICCAI (ID).

3.3. WML Segmentation: Out of Distribution

Next SC-UNET is trained using all 60 MICCAI volumes for the original and standardized data and tested on the held-out OOD clinical data from ADNI, CAIN and CCNA (128 volumes, approximately 5700 image slices). Example segmentations are shown in Figure 8 over all models and mean validation metrics are shown in Table 3. IAMLAB (0.64) and Ensemble (0.65) have the highest DSCs compared to the original (DSC = 0.60). Ensemble is also a top performer, with lowest EF (0.21) and H95 (11.21) and highest F1 score (0.60). Nyul has the highest Recall=0.76. When testing differences in DSC means, segmentation improvement afforded by intensity standardization was statistically different between original and all normalization methods, indicating segmentation improvement is significant.

To analyze the effect of IAMLAB and the Ensemble method on WML segmentation further, the change in DSC is plotted to investigate cases where segmentation was improved or hindered by normalization (Figure 3). The change in DSC is calculated by the DSC of the standardized model subtracted from the DSC of the model from original data for each volume. If there is a positive value, standardization improved performance while a negative value means it was more optimal to use original data and model. IAMLAB improved in 77% of the cases (98/128) and the Ensemble method improved in 86% of the cases, with only a few DSCs better in the original data. Examples of this are shown in Figure 6, for cases with an average negative DSC change of -0.12 (A, B, C) and cases with an average positive DSC change of 0.17 (D-J) for the IAMLAB standardized data model compared to a model from the original data. For WML segmentation problems, a small amount of improvement can be significant in terms of the segmentation result, since WML and the lesion loads can be small and missing a few pixels has a big impact on performance. The improvement over most of the cases indicates standardization improves generalization to the unseen sites (OOD).

A secondary analysis was conducted over lesion load ranges since the lesion load of the

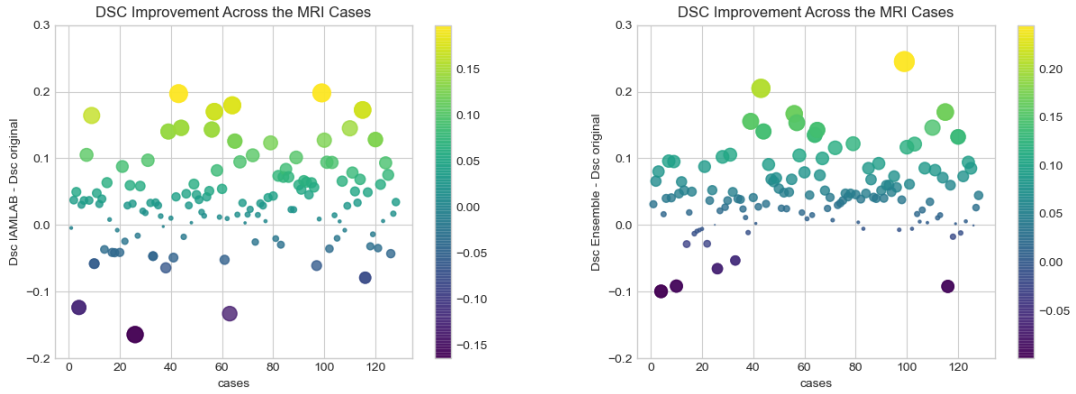

Figure 3: DSC Improvement in IAMLAB and Ensemble data compared to original

clinical data is low which may skew results. The dataset was divided into ranges as specified by the Fazekas scale (van Straaten EC, 2006), which approximately corresponds to 0-10mL, 10-25mL and 25+mL for Fazekas 1, 2 and 3, respectively. The small lesion load category is usually the most difficult for WML segmentation algorithms. Additionally, for small lesion

Table 3: WML segmentation performance on CCNA, CAIN, ADNI (N=128). **Bold** is the best and * indicates mean of the metric is significantly different from the original data using t-tests (p<0.05).

	DSC	EF	H95	AVD	F1-score	Recall
Original	0.60	0.21	13.44	35.16	0.56	0.69
Nyul	0.54	1.09	16.99	82.84	0.38	**0.76***
White-Stripe	0.62*	0.48	15.06	33.89*	0.53	0.73*
Z-Score	0.62	0.55	13.61	44.19	0.48	0.73*
IAMLAB	**0.64***	0.29	13.01	**24.35***	0.53*	0.71*
Ensemble	**0.65***	**0.21**	**11.21***	26.57*	**0.60***	0.69

loads, missing a small number of pixels can greatly reduce performance metrics such as the DSC. Segmentation performance for these lesion load ranges is summarized in Table 4, 5 and 6 and shown in Figure 9 -14.

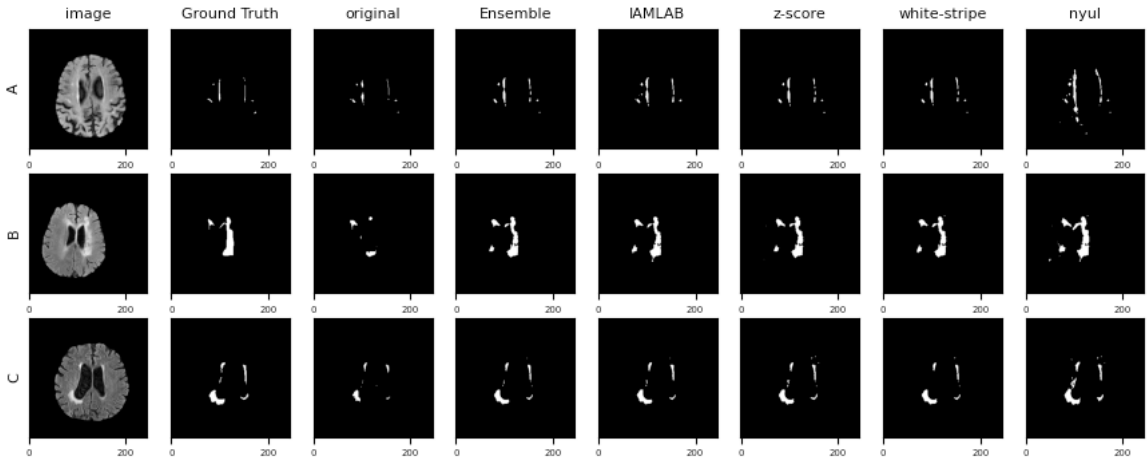

Figure 4: SC-UNET trained with MICCAI tested on ADNI (A), CAIN (B) and CCNA (C).

For LL <10mL, Ensemble has the highest DSC (0.55) and IAMLAB has the second highest DSC (0.53). Compared to the original data, DSC from IAMLAB and Ensemble are statistically different from the original data DSC, indicating the gains from using standardization on OOD data are significant. For 10-25mL, Ensemble method has the top DSC (0.67) and IAMLAB has the second highest DSC (0.66). DSC was statistically different than the original data for IAMLAB and Ensemble. For 25+mL, Ensemble had the highest DSC (0.77) by a large margin compared to the original data (0.71). While Ensemble, IAMLAB was the top performer and significantly different compared to the original data for the DSC, many metrics were optimal for standardized data. The original data had the lowest performance across the board in this lesion group. Out of all metrics, the original data was only the best in EF for 10-25mL and 25mL+ groups, which may be due to under-segmentation.

To investigate differences in normalization methods in terms of segmentation consistency, the coefficient of variation (CoV) of the DSC over different lesion loads are shown

in Figure 10. Ensemble and IAMLAB methods have the highest consistency (lowest CoV) which indicates that models developed on these datasets are more consistent and reliable. We postulate this is because these methods have better feature representation across imaging scanners due to overlapping intensity profiles of the imaging volumes. This is supported by the t-SNE feature representations in terms of the scanner type over all CCNA, CAIN and ADNI datasets (which are unseen, OOD) in Figure 7. There is more feature separation in the original data, and the clusters for each scanner type are more differentiated. In contrast, features are more overlapping in IAMLAB, White-stripe and Z-score indicating the same or similar features are being learned across the scanners in the standardized data. This suggests that intensity normalization minimizes the generalization gap between datasets for WML segmentation.

When taken all together, Ensemble and IAMLAB are the best performing algorithms on OOD for WML segmentation, which provides significant motivation for using these intensity normalization methods for segmentation of WML in multicentre FLAIR MRI; or when deploying algorithms on new scanners or sites to minimize the generalization gap. It is interesting to note that Ensemble and IAMLAB consistently provide the highest DSC and lowest H95, AVD. It seems these two algorithms are providing complimentary information for optimal segmentation on OOD datasets.

4. Conclusion

We investigate intensity normalization methods for deep learning-based WML segmentation methods on out-of-distribution FLAIR MRI datasets. An SC-UNET was trained using MICCAI competition data for the original dataset along with the four normalization methods. Models were tested on a diverse OOD test set from four different datasets comprising 128 imaging volumes. It was observed that intensity normalization using IAMLAB and the ensemble segmentation from IAMLAB, White-Stripe and Z-score normalization models leads to a statistically significant improvement in segmentation performance on OOD data. Therefore, IAMLAB and Ensemble methods are excellent candidates to improve generalization across clinical datasets from different centers, which is key for translation.

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Appendix A. Intensity Standardization

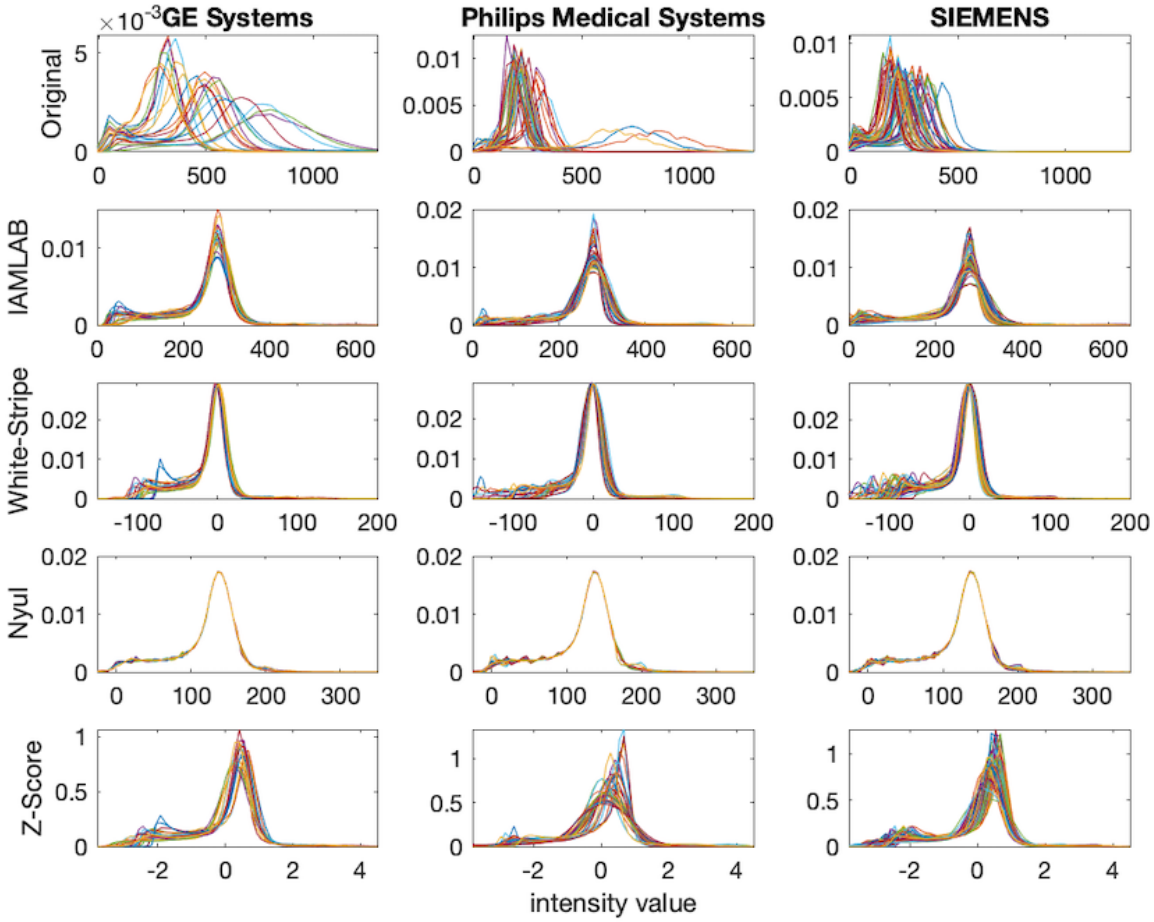

Figure 5: Whole Brain histograms of 128 volumes over all normalization methods.

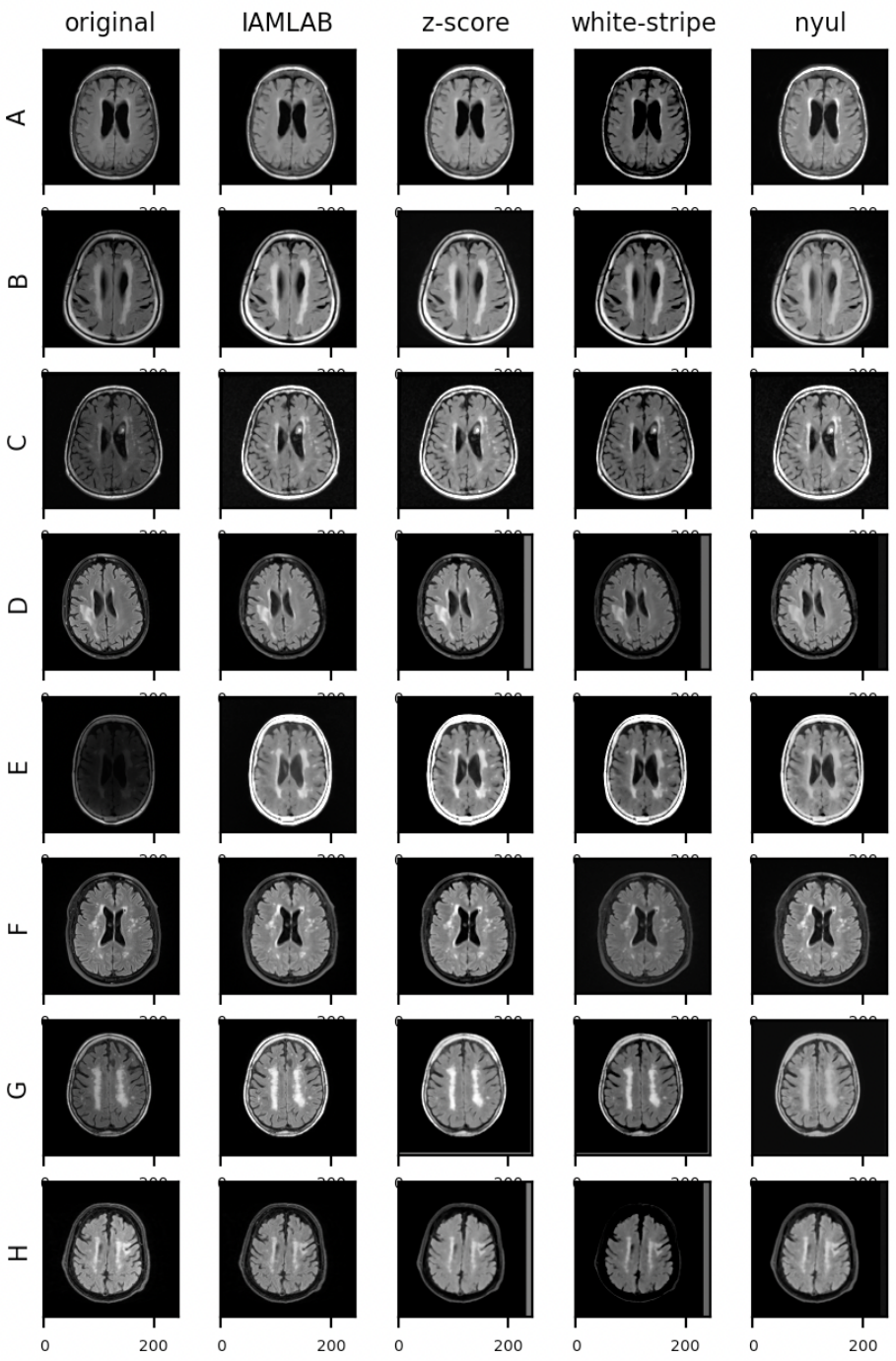

Figure 6: FLAIR MRI slices on 245x245 regions for original and all standardization. Images are from ADNI (A,B), CAIN (C,D) and CCNA (E,F) and MICCAI17 (G,H).

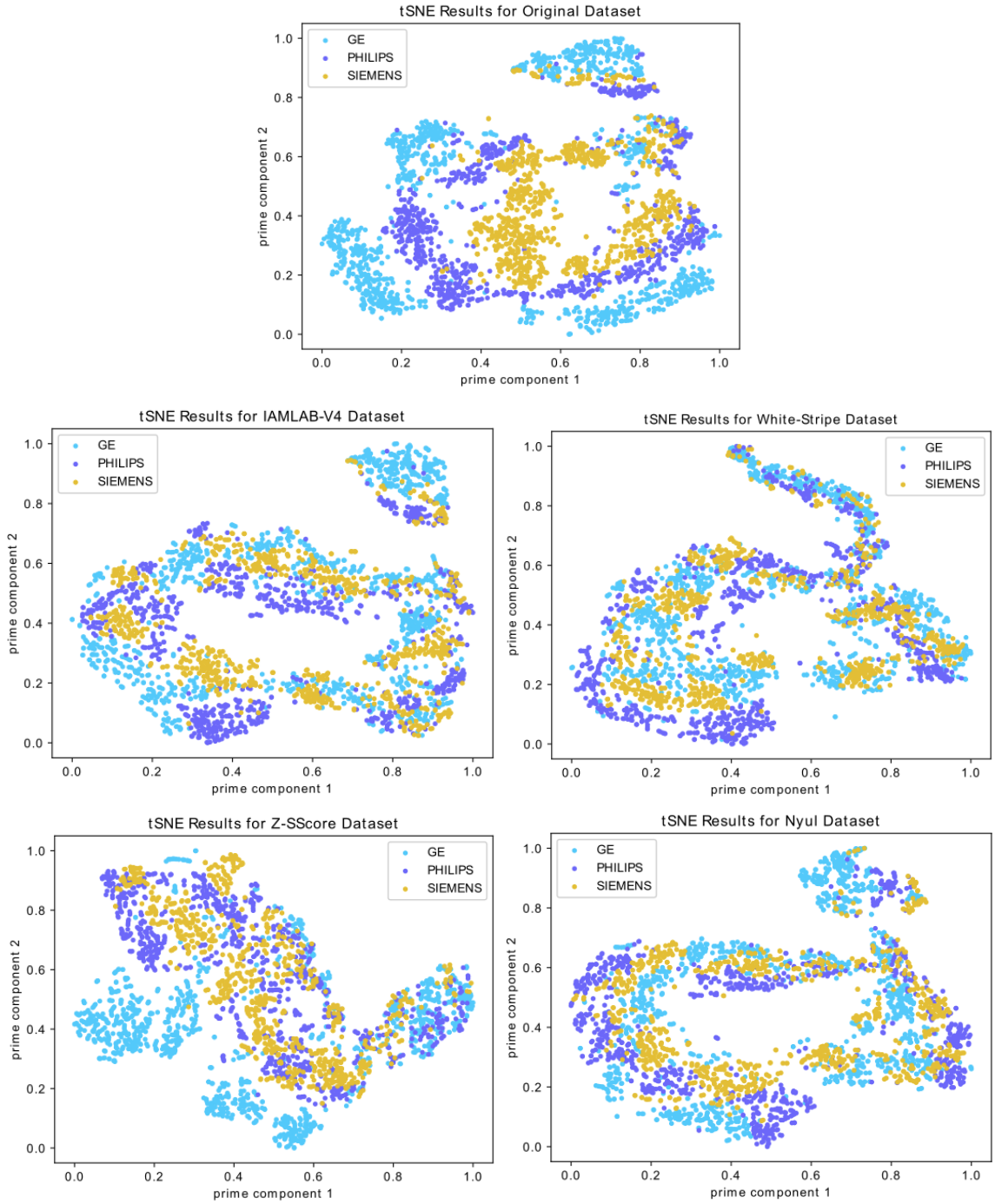

Figure 7: t-SNE representations for all data for original and standardized versions.

Appendix B. WM Lesion Segmentation Results

Figure 8: WML segmentation results on 145x145 regions for original and all normalizations. Images are from ADNI (A,B, C), CAIN (D,E,F,G) and CCNA (H,I,J).

Table 4: Segmentation performance on CCNA, CAIN, ADNI: LL<10mL (N=51)

	DSC	**EF**	**H95**	**AVD**	**F1-score**	**Recall**
Original	0.521	0.279	16.407	42.464	0.550	0.713
Nyul	0.405	1.900	23.759	156.976	0.278	**0.792***
White-Stripe	0.515	0.734	21.647	54.956	0.482	0.738
Z-Score	0.500	0.879	19.098	79.484	0.437	0.735
IAMLAB	0.532*	0.376	18.569	**33.882**	0.492	0.705
Ensemble	**0.554***	**0.246**	**15.896**	36.018	**0.566**	0.689

Table 5: Segmentation performance on CCNA, CAIN, ADNI. LL: 10-25mL (N=45)

	DSC	**EF**	**H95**	**AVD**	**F1-score**	**Recall**
Original	0.617	**0.183**	12.617	34.200	0.586	0.698
Nyul	0.578	0.686	14.486	41.776	0.440	**0.769***
White-Stripe	0.654	0.348	11.693*	23.977*	0.586	0.733*
Z-Score	0.648	0.388	11.254*	25.848*	0.531	0.735
IAMLAB	0.663*	0.257	10.262*	**19.633***	0.589*	0.727*
Ensemble	**0.669***	0.195	**9.009***	23.316*	**0.639**	0.697

Table 6: Segmentation performance on CCNA, CAIN, ADNI. LL: 25mL+ (N=32)

	DSC	**EF**	**H95**	**AVD**	**F1-score**	**Recall**
Original	0.705	**0.148**	9.857	24.879	0.527	0.662
Nyul	0.709*	0.369	9.735	22.428*	0.441	0.687
White-Stripe	0.749*	0.242	9.312	14.242*	0.516	0.702
Z-Score	0.759*	0.243	8.173*	**13.739***	0.484	**0.704**
IAMLAB	0.762*	0.202	8.034*	15.782*	0.523	0.698
Ensemble	**0.766***	0.154	**6.820***	16.105*	**0.592***	0.677

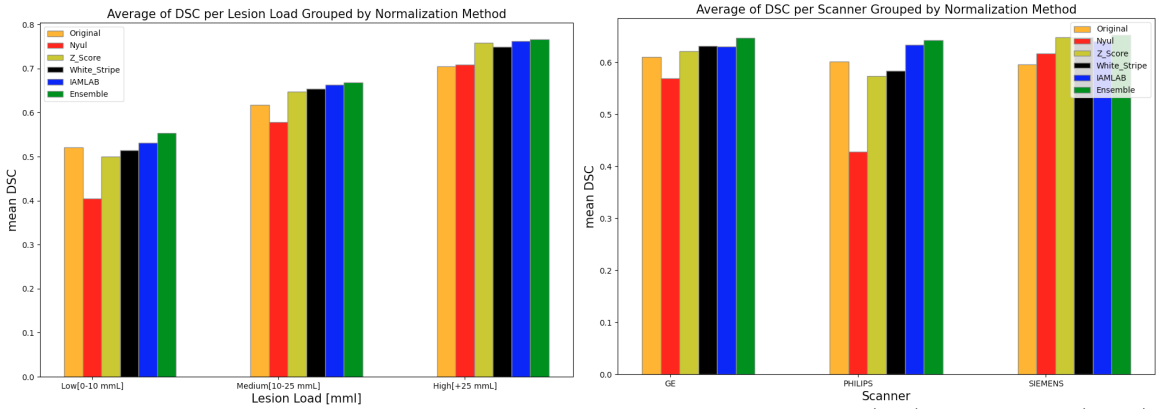

Figure 9: Mean DSC metric from CAIN, CCNA and ADNI over lesion load (left) and scanner (right) group for different normalizations.

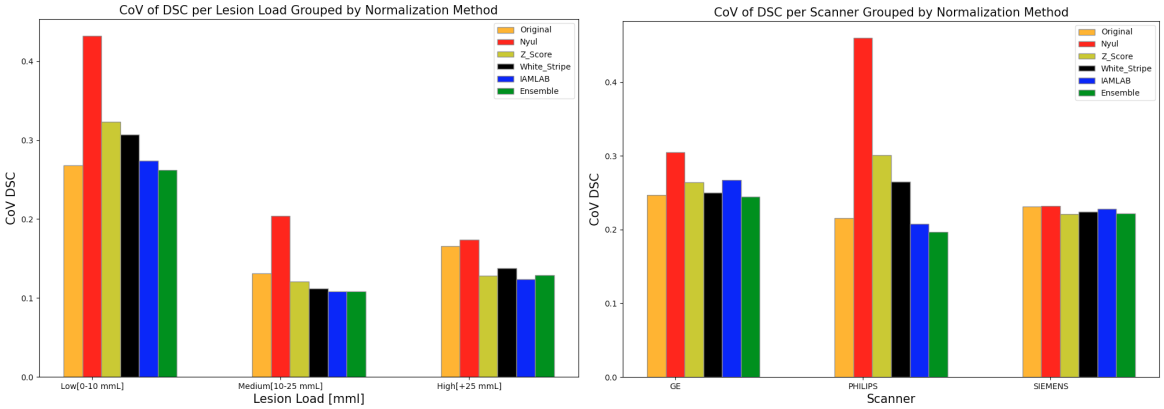

Figure 10: CoV of DSC metric from CAIN, CCNA and ADNI over lesion load (left) and scanner (right) group for different normalizations.

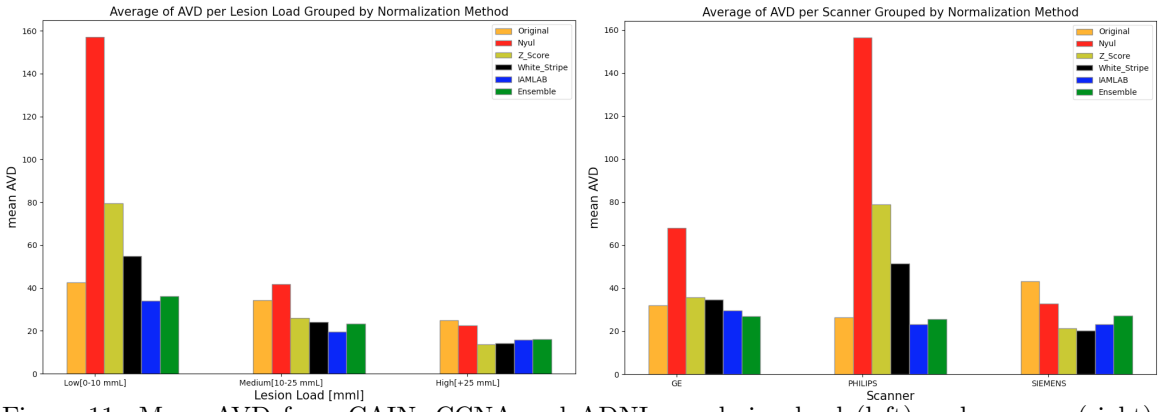

Figure 11: Mean AVD from CAIN, CCNA and ADNI over lesion load (left) and scanner (right) group for different normalizations.

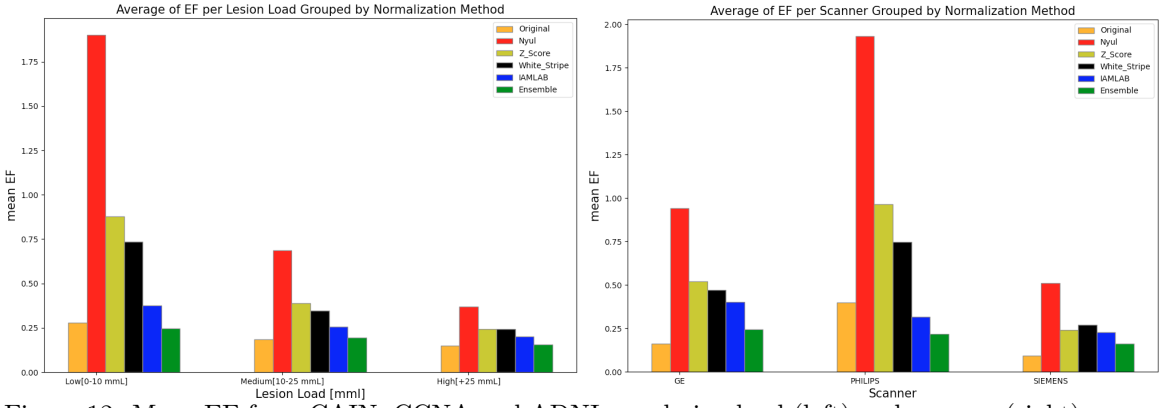

Figure 12: Mean EF from CAIN, CCNA and ADNI over lesion load (left) and scanner (right) group for different normalizations.

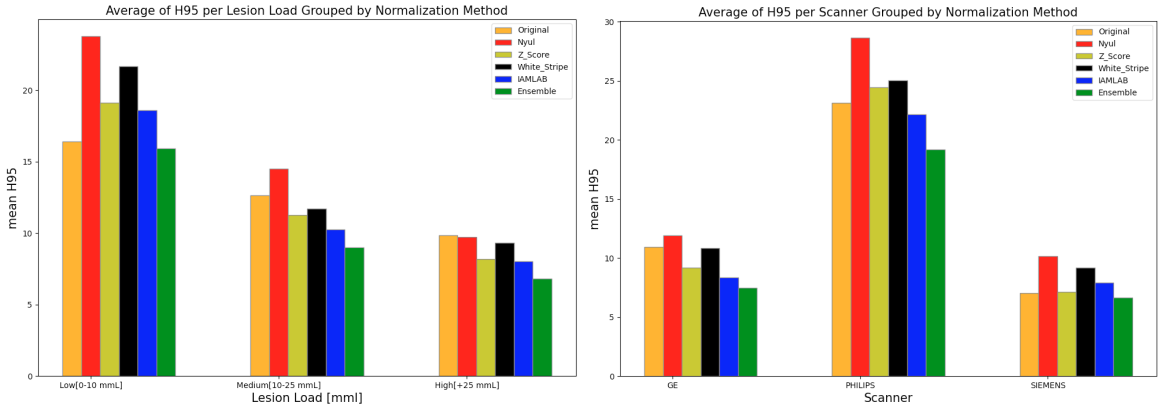

Figure 13: Mean H95 metric from CAIN, CCNA and ADNI over lesion load (left) and scanner (right) group for different normalizations.

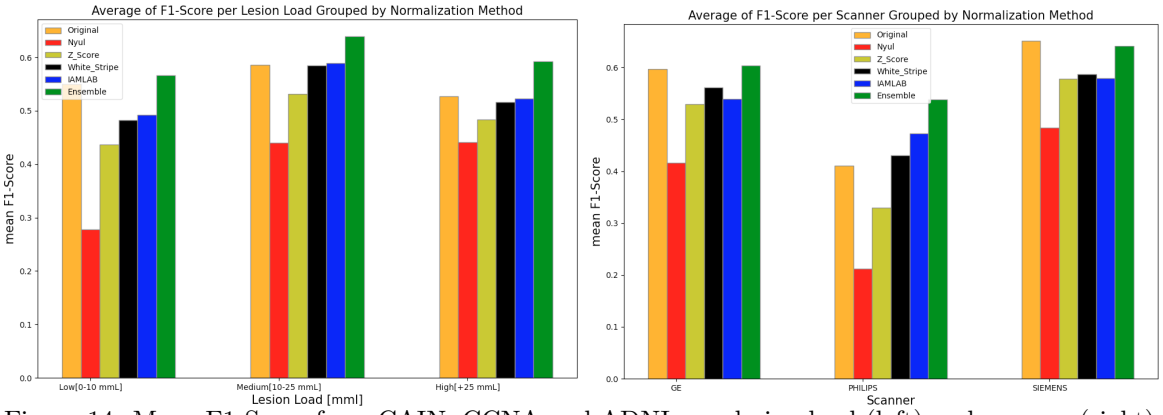

Figure 14: Mean F1-Score from CAIN, CCNA and ADNI over lesion load (left) and scanner (right) group for different normalizations.