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Repeatability of Radiomic Features in Magnetic Resonance Imaging of Glioblastoma: Test-Retest and Image Registration Analyses

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ABSTRACT

Purpose: To assess repeatability of radiomic features in magnetic resonance (MR) imaging of glioblastoma (GBM) tumors with respect to test-retest, different image registration approaches and inhomogeneity bias field correction.

Methods: We analyzed MR images of 17 GBM patients including T1 and T2-weighted images (performed within the same imaging unit on two consecutive days). For image segmentation, we used a comprehensive segmentation approach including entire tumor, active area of tumor, necrotic regions in T1-weighted images, and edema regions in T2-weighted images (test studies only; registration to retest studies is discussed next). Analysis included N3, N4 as well as no bias correction performed on raw MR images. We evaluated 20 image registration approaches, generated by cross-combination of 4 transformation and 5 cost function methods. In total, 714 images (17 patients × 2 images × ((4 transformations × 5 cost functions) + 1 test image) and 2856 segmentations (714 images × 4 segmentations) were prepared for feature extraction. Various radiomic features were extracted, including the use of pre-processing filters, specifically wavelet (WAV) and Laplacian of Gaussian (LOG), as well as discretizations into fixed bin width and fixed bin count (16, 32, 64, 128 and 256), Exponential, Gradient, Logarithm, Square and Square Root scales. Intra-class correlation coefficients (ICC) were calculated to assess repeatability of MRI radiomic features (high repeatability defined as ICC ≥ 95%).

Results: In our ICC results, we observed high repeatability (ICC ≥ 95%) with respect to image preprocessing, different image registration algorithms and test-retest analysis, for: RLNU and GLNU from GLRLM, GLNU and DNU from GLDM, Coarseness and Busyness from NGTDM, GLNU and ZP from GLSZM, and Energy and RMS from first order. Highest fraction (percent) of repeatable features were observed, amongst registration techniques, for the method Full Affine transformation with 12 degrees of freedom using Mutual Information cost function

(mean 32.4%), and amongst image processing methods, for the method Laplacian of Gaussian (LOG) with Sigma (2.5-4.5 mm) (mean 78.9%). The trends were relatively consistent for N4, N3 or no bias correction.

Conclusion: Our results showed varying performances in repeatability of MR radiomic features for GBM tumors due to test-retest and image registration. The findings have implications for appropriate usage in diagnostic and predictive models.

Keywords: Radiomics, MRI, Test–retest, Repeatability, Glioblastoma, Image registration, bias correction.

INTRODUCTION

Glioblastoma multiform (GBM) is a very heterogeneous cancer with poor prognosis and treatment outcome [1]. The median survival for GBM patients is about 15 months and its occurrence rate is two or three cases per 100,000 per year [2]. Surgical resection followed by radiotherapy and chemotherapy is the current standard approach to treat GBM [3]. In this context, magnetic resonance imaging (MRI) plays a critical role in clinical diagnosis and treatment, particularly towards informed surgery and radiotherapy treatment planning [3].

For years, qualitative MR image sequences have been used for GBM management. In recent years, quantitative image-derived so-called radiomic features extracted from standard MR images have been increasingly studied as powerful prognostic tools to enhance patient management through improved stratification [4]. Studies have identified that MR image features extracted from GBM tumors are highly correlated with tumor heterogeneity, response failure and survival[5-7], metastasis and genomic parameters[8-11] (as reviewed in [12]).

Radiomics is an active area of research, aiming to quantify images using different feature categories towards improved clinical tasks [13-17]. In radiomics studies, a wide range of features are extracted from high quality images for several applications, such as clinical correlations, therapy response prediction, tumor characterization and survival assessment [18-21]. Radiomics is a multi-step process applied to medical images involving image segmentation, feature extraction, feature selection and multivariate analysis[21,22]. Variations in these main steps and their sub-steps, may result in notable alterations in radiomic features as considered for final outcome analysis. Although radiomic analyses are becoming increasing mature, there are a number of important technical limitations, and many radiomic features are vulnerable to significant variations based on image acquisition, reconstruction and processing methods, as reported by ongoing radiomics studies [23-27]. Moreover, as hundreds of feature sets are available for consideration in medical imaging, it is necessary to consider the reproducibility and repeatability of radiomic features as a feasible measure to pre-select features for further analysis, such as classification and clinical correlation [23].

In image biomarkers development, there are two main frontiers which should be assessed in regard to robustness of radiomic features. Specifically, repeatability and reproducibility of radiomic features can be important towards discovery of high-performance image biomarkers for using in preclinical or clinical settings. The Quantitative Imaging Biomarker Alliance (QIBA) Technical Performance Working Group has defined repeatability as the "variability of the image biomarker when repeated measurements are acquired on the same experimental unit under identical or nearly identical conditions" and reproducibility as "the variability in the image biomarker measurements associated with using the imaging instrument in real world clinical settings which are subject to a variety of external factors that cannot all be tightly controlled" [28].

Although a number of studies have been conducted on repeatability and reproducibility of radiomic features in different imaging modalities, some issues remain to be explored, particularly for MRI radiomic features in GBM cancer [29,30]. Gourtsoyianni *et al*. [31] assessed day-to-day repeatability of global and local regional MR imaging texture features derived from primary rectal cancer, and demonstrated that repeatability is higher for global texture parameters relative to local-regional texture parameters, indicating that global texture parameters should be sufficiently robust for clinical practice. Baessler *et al*. [32] investigated the robustness of radiomic features in different MRI sequences. In that study, a phantom was scanned on a clinical 3T system using FLAIR, T1w, and T2w sequences, and scans were repeated after repositioning of the phantom. The study showed that only 15 of 45 features had good robustness across all MRI sequences. Including repeatable features in diagnostic and predictive models can be key for ensuring model generalizability [33-35]. As such, the present study focuses on the study of repeatability, but in a novel context of studying image registration methods for mapping retest images to test images. As image registration plays a critical role in several clinical settings, such as treatment planning, we studied the temporal variations of MR imaging features in two consecutive days.

MATERIAL AND METHODS

Figure 1 illustrates the various processes followed in this work, as elaborated below. Repeatability assesses feature variability in the context of varying imaging times (test-retest) under otherwise similar processes.

Patient data

We included 19 patients with pathologically confirmed GBM. The RIDER NEURO MRI [36] dataset were obtained from the cancer imaging archive (TCIA) [36,37] were used for this study. All patients had two MR images, including T1- (gradient echo (GRE), gadolinium enhanced) and T2- (fluid attenuation inversion recovery (FLAIR), gadolinium enhanced) weighted sequences which had been acquired in two consequent days with the same protocols on a 1.5 tesla MRI scanner (Siemens Healthcare, SYNGO MR 2004V 4VB11D). Image acquisition and reconstruction parameter details were presented in Table 1. After reviewing all images, two patients were excluded: one patient because of challenges on finding the tumor, and another patient because of missing second day images. Finally, we analyzed MR images of 17 (two patients were excluded from 19 patients because of low image quality and miss one the image sequence) GBM patients including T1 and T2-weighted images.

Image segmentation

We performed all image segmentations manually using the open source software ITK-Snap [38]. For image segmentation, we used a comprehensive segmentation approach based on BRATS[39,40] including a) entire tumor (enhancing + necrotic core), b) active area of tumor (enhancing core), c) necrotic regions (necrotic core) in T1-weighted images, and d) edema regions (edema core) in T2-weighted images (test studies only; registration to retest studies is discussed next). In total, the following segmentations were obtained per patient: 3 segmentations in the T1 weighted image, and 1 segmentation in the T2 weighted image. This was followed by reciprocal transfer of segmentations from T1 (T2) to T2 (T1) weighted images, arriving at 8 segmentations in total (4 on T1 and 4 on T2) for each patient.

Image registration

Each segmentation performed above for a given patient image was naturally mapped to the subsequent follow-up image following image registration of retest images to test images. Overall, we performed 20 types of image registrations obtained by cross combination of 4 transformations and 5 cost function methods, using Mango open source software [41]. For transformation, we applied full affine (FA), full scale (FS), global scale (GS) and rigid-body (RB) with 12, 9, 7 and 6 degrees of freedom (DOF), respectively. Cost functions consisted of correlation ratio (CR), mutual information (MI), normalized mutual information (NMI), normalized correlation (NC) and least squares (LS).

Feature extraction

In total, 714 images (17 patients × 2 images × ((4 transformations × 5 cost functions) + 1 test image))) and 2856 segmentations (714 images × 4 segmentations) were prepared for feature extraction. The N3[42] and N4[43] bias correction methods were additionally applied on raw MRI images. For pre-processing, we applied filters including wavelet (all possible combinations of applying either a high or a low pass filter in each of the three dimensions, including HHH, HHL, HLH, HLL, LHH, LHL, LLH and LLL)) and Laplacian of Gaussian (LOG) with different sigma values (0.5 to 5 with steps 0.5) all with 64 bins. Subsequently, images were discretized into 16, 32, 64, 128 and 256 fixed bin count and fixed bin widths, Exponential, Gradient, Logarithm, Square and Square Root scales. Three types of features, namely first-order, shape-based and textural features, were then extracted. Texture sets consisted of gray level co-occurrence matrix (GLCM), gray level run length matrix (GLRLM), gray level dependence matrix (GLDM), gray level size zone matrix (GLSZM) and neighboring gray tone difference matrix (NGTDM). In sum, more than twenty-six million (26,295,192) features were extracted from the original as well as N3 and N4 bias corrected images for further analysis. Details on image features are shown in Supplementary Table 1. Different tools have been developed for extraction of radiomics feature [44-47]. Our current study performs mage feature extraction using the Python library PyRadiomics [44] which the feature definition is compliant with the Image biomarker standardization initiative (IBSI) . As an exception, the definition of Kurtosis from first order features differs between PyRadiomics and IBSI. IBSI and PyRadiomics calculates Kurtosis with –3 and +3 respectively, and this stem from the fact that a gaussian distribution has a kurtosis.

Statistics and data analysis

In the present work, we used applied intra-class correlation coefficient (ICC) test for analysis of feature repeatability.

The intra-class correlation coefficient (ICC) is a widely used reliability index in test-retest, interrater and interrater reliability analyses. ICC can be defined as follows:

$$ICC = \frac{MS_R - MS_W}{MS_R + (k-1)MS_W} \quad \text{Eq. 1}$$

where MS_R denotes mean square for rows (each feature value in test and retest), MS_W indicates mean square for residual source of variance, k is the number of observers involved, and n is the number of subjects.

Based on ICC, robust features were categorized into five categories, namely 1) ICC <50%, 2) 50% < ICC < 80%, 3) 80% < ICC < 90%, 4) 90% < ICC < 95% and 5) ICC > 95%. Features with ICC > 95% were defined as highly robust features. For comparison of image registration methods, we reported the peak value of the probability density function for each feature set. The R package, version 3.1.3 IRR, was used for ICC computations.

ICC results are shown by the probability density distribution (PDD), which is used to provide quantitative statistical description of ICC. In PDD, shape, and peak value can be used to compare the ICC results. Specifically, in our work, we use this framework to assess how radiomic features are impacted against different image registration methods in the test-retest setting.

RESULTS

Analyzing the large set of radiomic features obtained from image types, different bias corrections, image registrations, regions, as well as pre-processing and feature sets, here we report the most relevant findings, while other findings are presented as supplementary data.

Figure 2 illustrates ICC values (categorized 1 to 5: 1 = low and 5 = highly robust) of radiomic features as extracted from discretization with 64 gray level fixed bin width for different image registration algorithms (N4 bias corrected images). The ICC values for all shape features were found to be more than 95% due to the fact that same segmentations in test images were mapped onto retest images. As such, these features were excluded from further analysis. Several first-order (FO) features including RMS, Mean, TE, Energy and 90Percentile and RLNU from GLRLM had ICC > 95%. In addition, for Laplacian of Gaussian (LOG) with Sigma (3.5 mm) and Wavelet with LLL decomposition preprocessing, as used prior to extraction of radiomic features (Figures 3 and 4 in N4 bias corrected images, respectively), the above-mentioned FO features were found to be robust. On the other hand, as shown in Figure 3, certain features including GLCM (CP, CT, IV, SS), GLDM (DNU, GLNU, GLV, SDE, SDHGLE), GLRLM (GLNU, GLV, RLNU), GLSZM (GLNU, SZNU, ZP), NGTDM (Busyness, Strength), were commonly robust to different image registration algorithms. Also, as shown in Figure 4, certain features including GLCM (DE), GLDM (DNU, GLNU), GLRLM (GLNU, RLNU), GLSZM (GLNU, ZP) were highly robust to different image registration algorithms. Supplemental Tables 2, 5 and 8 present the percent of each ICC group (for different image registration and image processing settings) for the original as well as N4 and N3 bias corrected images, respectively. Supplementary Tables 3 and 4 show the highest (ICC>95%) and lowest repeatable features (ICC<50%), respectively, for original images in different image processing and registration settings. Supplementary Tables 6 and 7 show these for N4 bias corrected images, while Supplementary Tables 9 and 10 show them for N3 bias corrected images. The other results for ICC values, including heat maps for fixed bin count (16, 32, 64, 128, 256), fixed bin width (16, 32, 128, 256), Exponential, Gradient, Logarithm, Square, Square Root, LOG and Wavelet are presented as supplementary Figures 1-17 and 18-33 and 33-50 for the original, N4 and N3 bias corrected images, respectively.

In Figure 5-a, we present bar plots depicting percent of five ICC categories for different image preprocessing methods (across all radiomic features and registration algorithms) in N4 bias corrected images. The results show LOG pre-processing with medium sigma (2.5-4.5 mm) with highest fraction (percent) of robust features (mean 78.9%). In addition, Figure 5-b depicts ICC bar plots of different registration methods (across all radiomic features and image preprocessing methods) for N4 bias corrected images. As shown, the FA method with MI cost function (mean 32.4%) vs. GS registration method with LS cost function (mean 18.8%) depicted highest vs. lowest fraction (percent) of robust features, respectively. Similar bar plots for Original and N3 Bias Corrected images are presented in supplementary Figures 75 and 77, respectively.

In Supplementary Figures 63-66, 67-70 and 71-74, we illustrate bar plots of ICC groups for radiomic features against applied registration algorithms for the original, N4 and N3 bias corrected images, respectively. Interestingly, it is seen that the reproducibility performances for each of these 3 sets of images (i.e. Original, N3 and N4) are relatively consistent with respect to one another. Specifically, Supplemental Figure 69 depicts LOG pre-processing filter in N4 Bias Corrected images, arriving at highest number of reproducible features amongst preprocessing methods. As also seen, FA method with MI cost function provided highest number of reproducible features (10.8-79.6% depending on LOG sigma value; optimized for 2.5-4.5mm), and GS method with LS methods depicted lowest (5.4-36.6%) number of reproducible features. Supplementary Figures 75 and 77 show ICC Bar plots for the original and N3 bias corrected images, respectively, for different image preprocessing methods (across all radiomics feature and registration algorithms), different registration methods (across all radiomic features and image preprocessing methods), and different features (across all radiomic features and image preprocessing methods), arriving at generally similar observations.

Supplementary Figure 76 show ICC bar plots of different features in N4 bias corrected images (different image preprocessing and registration algorithm). ICC results showed high repeatability for RLNU (90.8%) and GLNU (88.8%) from GLRLM, GLNU (76.1%) and DNU

(69.2%) from GLDM, Coarseness (65.8%) and Busyness (54.9%) from NGTDM, GLNU (57.4%) and ZP (39.7%) from GLSZM, and Energy (65.5%) and RMS (64.9%) from first order were most highly repeatable with respect to image preprocessing and different image registration algorithms and test-retest analysis (ICC>95%). Correlation (24.4%) and AC (22.7%) from GLCM, HGLZE (22.9%), LAE (22.6%) and ZV (22.5%) from GLSZM, HGLRE (22.7%) from GLRLM, and HGLE from GLDM (22.7%) had lowest reproducibility with respect to image preprocessing, different image registration algorithms and test-retest analysis (with ICC<50%).

Figure 6-a shows ICC bar plots between Original and N3 bias corrected images (across all radiomic features and registration algorithms). All preprocessed images except Fixed Bin Width (FBW) had high reproducibility. Figure 6-b ICC shows bar plots between Original and N4 bias corrected images (across all radiomic features and registration algorithms). It is essentially seen that N4 bias correction alters images more significantly than N3, with respect to Original images. Nonetheless, as discussed above, reproducibility performances within these 3 sets of images (Original, N3 and N4), are relative consistent with respect to one another.

Figure 7 (a-f) depicts the probability density of ICC distribution for different types of radiomic features in N4 bias corrected images. The ICC distributions are different in several aspects, including peak values, ICC distribution per image registration method and density values. In Figure 7 (a-b), the main peak values of probability density for fixed bin count and fixed bin width discretized radiomic features (64 bin discretization) are ≥ 5, while in Figure 7 (c and d), the peak values of features (Square and Square Root) are ≥ 5. For LOG features (Figure 7 e), the peak values of probability density are more than 18, while for Wavelet features, these values are more than 7.5. More details about the probability density plot are presented in supplementary Figures 51-54, 55-58 and 59-62 for the original, N4 and N3 bias corrected images, respectively.

Table 2 shows our results for highly repeatable features (ICC ≥ 0.95) against different registration schemes for N4 bias corrected images (the highest value in each row is set to bold). For all feature sets, highly repeatable features were found for the registration method FA-MI (range; 17.2-32.3% for BIN, 10.8-79.6% for LOG & 6.45-45.2% for wavelet). For LOG features, the highest repeatability was found for the RB-NMI registration scheme (82.8%). More details on repeatability are provided in supplementary Tables 2, 5 and 8 for the original, N4 and N3 bias corrected images, respectively. The results for features with ICC>95% and ICC<50% against all registration methods are summarized in supplementary Tables 3-4,6-7 and 9-10 for original, N4 and N3 Bias corrected images, respectively. The number of high

reproducible features (ICC>95%) were 243, 358 and 268 for Original, N4 bias corrected and N3 Bias corrected images, respectively (across all radiomic features, image preprocessing methods and registration algorithms).

DISCUSSION

The assessment of repeatability and reproducibility for image features has garnered increasing interest [29]. Accumulating evidence suggests the importance of taking such analyses into account. Studies have emphasized that repeatable radiomic features must be used for predictive modelling [31]. In the present study, we aimed to assess test-retest repeatability of MRI radiomic features in GBM cancer patients as well as their repeatability against a wide range of image registration schemes. Different tools have been developed for radiomics feature extraction[44-46]; our study was conducted using the PyRadiomics package according to consensus definitions of the Image biomarker standardization initiative (IBSI) [48,49]. IBSI is an independent international collaboration working towards standardization of image biomarkers. In this approach, all image features are standardized in terms of definitions, image processing, and reporting system.

In our ICC results, we observed high repeatability (ICC ≥ 95%) with respect to image preprocessing, different image registration algorithms and test-retest analysis for: RLNU and GLNU from GLRLM, GLNU and DNU from GLDM, Coarseness and Busyness from NGTDM, GLNU and ZP from GLSZM, and Energy and RMS from first order features. In addition, several first-order wavelet and LOG were found to be high-ICC features (supplementary Figures 15-16). As comparison, Schwier *et al.* [50] recently also reported that first-order features Mean and Median had ICC ≥ 95% in prostate MR image feature test-retest analysis.

Image registration is a key consideration in treatment response evaluation and adaptive radiotherapy. Our analysis shows that different image registration schemes have different effects on radiomic features. Depending on registration settings including transformation and cost function, feature performances vary. Highest percent of repeatable features were observed, amongst registration methods for the method Full Affine with 12 degrees of freedom with Mutual Information cost function (mean 78.9%), and amongst image processing methods for the method Laplacian of Gaussian (LOG) with Sigma (2.5-4.5 mm) (mean 32.4%).

There are a number of feature robustness analysis studies indicating that radiomic feature values vary with image acquisition and reconstruction parameters. Ford *et al.* [51] studied the impact of pulse sequence parameter selection on MRI-based textural features of the brain. Pulse sequences consisted of spin echo (SE), gradient echo (GRE), spoiled gradient echo (SP-GRE), inversion recovery spin echo (IR-SE), and inversion recovery gradient echo (IR-GRE). They found that radiomic features varied considerably among images generated by the five different T1-weighted pulse sequences, and that deviations from those measured on the T1 map varied

among features, from a few percent to over 100%. Yang *et al.* [52] examined the dependence of image texture features on MR acquisition parameters and reconstruction using a digital MR imaging phantom. They studied the effects of varying levels of acquisition noise, three acceleration factors, and four image reconstruction algorithms on MRI features. The investigators observed feature variance due to reconstruction algorithm and acceleration factor to be generally smaller than the clinical effect size. In that study, it was suggested that adequate precautions need to be taken regarding the validity and reliability of texture features, although some features had been preserved by changes in MR imaging settings. Molina *et al*. [53] studied potential variations of textural measures due to changes in MRI protocols including four different spatial resolution combinations and three dynamic ranges. The results showed that no textural measures were robust under dynamic range changes and entropy was the only textural feature robust under spatial resolution changes. Imaging-based changes including acquisition and reconstruction should be considered and separated from therapy related and tumor biological changes. In our study, we observed that several radiomic features change significantly across scan times.

Other researchers have attempted to assess robustness of radiomic features in different imaging modalities including CT. Cunliffe *et al*. [54] demonstrated that registration altered the values of the majority of CT texture features. They applied their texture analysis on serial CT scans and showed that 19 features remained relatively stable after demons registration, indicating their potential for detecting pathologic change in serial CT scans. They also indicated that combined use of accurate deformable registration using demons and texture analysis may allow quantitative evaluation of local changes in lung tissue due to disease progression or treatment response. Chou *et al*. [55] evaluated radiomic features stability when deformable image registration was applied. They applied feature analysis on lung cancer four-dimensional computed tomography (4DCT), and deformable image registration (DIR) was applied between the inspiration and expiration phases of 4DCT datasets. They concluded that many features were unstable (mean variation > 50% or CCC < 0.5) when DIR is applied, caution is needed in radiomic feature analysis when DIR is necessary.

A recent study performed by Lv *et al* [56] in nasopharyngeal PET/CT showed that some radiomic features even with low ICC may perform well in disease discrimination. They demonstrated that poor absolute scale reproducibility of radiomic features did not necessarily translate into poor disease differentiation. In other words, features may change significantly due to different kinds of processing, but their relative ordering may remain the same. Nonetheless, this was a reproducibility study: in repeatability studies (including the present

work where for a given processing, test-retest values of features are evaluated), including high-ICC repeatable radiomic features in diagnostic and predictive models may be critical for model generalizability.

Low frequency intensity non-uniformity presence in MR images, defined as field bias, could confound performance. To address this bias, different algorithms have been proposed including N3[42] and N4 bias correction[57]. In the present study, we used N3 and N4 bias correction and found that these algorithms had considerable impact on radiomic features. In reference to no bias correction, N3 bias correction produced higher number of reproducible features compared to the N4 algorithm, i.e. N3 algorithm had less impact on radiomics features with respect to non-bias corrected images. In addition, we identified that LHL decomposition from wavelet vs. exponential (as well as 64 fixed bin width) pre-processing led to highest vs. lowest number of reproducible features, respectively.

Harmonization is also a critical issue in radiomics studies [58]. Several studies have indicated that image features have to be harmonized against parameters which have great impact on feature values, such as scanner variations, reconstruction, imaging protocols [59-61] . In our study, all images were acquired on the same scanner using the same imaging protocol. As such, there was no need to harmonize image features, yet studies are needed to test or investigate methods to harmonize features in test-retest and registration methods. With regards to harmonization, Hu *et al* [62] demonstrated that normalized features have more stability [62]. In addition, Orlhac *et al* [60] showed that harmonization can be efficient at removing multicenter effects on textural features.

Treatment response evaluation in GBM suffers from several uncertainties in differentiation among pseudo-progression, pseudo-response, treatment related necrosis and true progression [63,64]. Although, single imaging studies have found feasible results, several studies have indicated that diagnosis of pseudo-progression could not be achieved by a single imaging technique and suggested that serial imaging will results in improved diagnosis accuracy [65,66]. On the other hand, there are several variations in the clinical definitions of pseudo-progression based on the imaging reports which requires higher-precision quantitative imaging [67]. Some radiomics studies have shown feasibility of MR image radiomic features to discriminate between pseudo-progression compared to true progression [68-70] and genomic mutation prediction[8-11,71,72] and treatment response assessments[5,6]. In the present image biomarker discovery era, our results would be important, wherein radiomic features with greatest robustness to image registration between images may be more beneficial in clinical studies. Specifically, because studies have suggested serial imaging for treatment response evaluation,

serial radiomic studies may benefit by integrating the identified robust radiomic features and methods as candidate biomarkers for GBM response assessment and prediction.

The limitation of this work is mainly the number of patients. The results of this study should be confirmed in a larger, multi-center dataset. In addition, the present work can be extended to other types of MR images, including diffusion weighted and dynamic contrast enhanced, and in other organs and diseases.

CONCLUSION

Repeatable radiomic features are potentially better candidates for usage in diagnostic and predictive models. Our results showed varying performance in repeatability of MR radiomic features for GBM tumors due to test-retest and image registration. The trends were relatively consistent for N4, N3 or no bias correction. Full Affine with 12 degrees of freedom with Mutual Information cost function and Laplacian of Gaussian (LOG) image processing resulted in highest percent of repeatable features in image registration and image processing, respectively.

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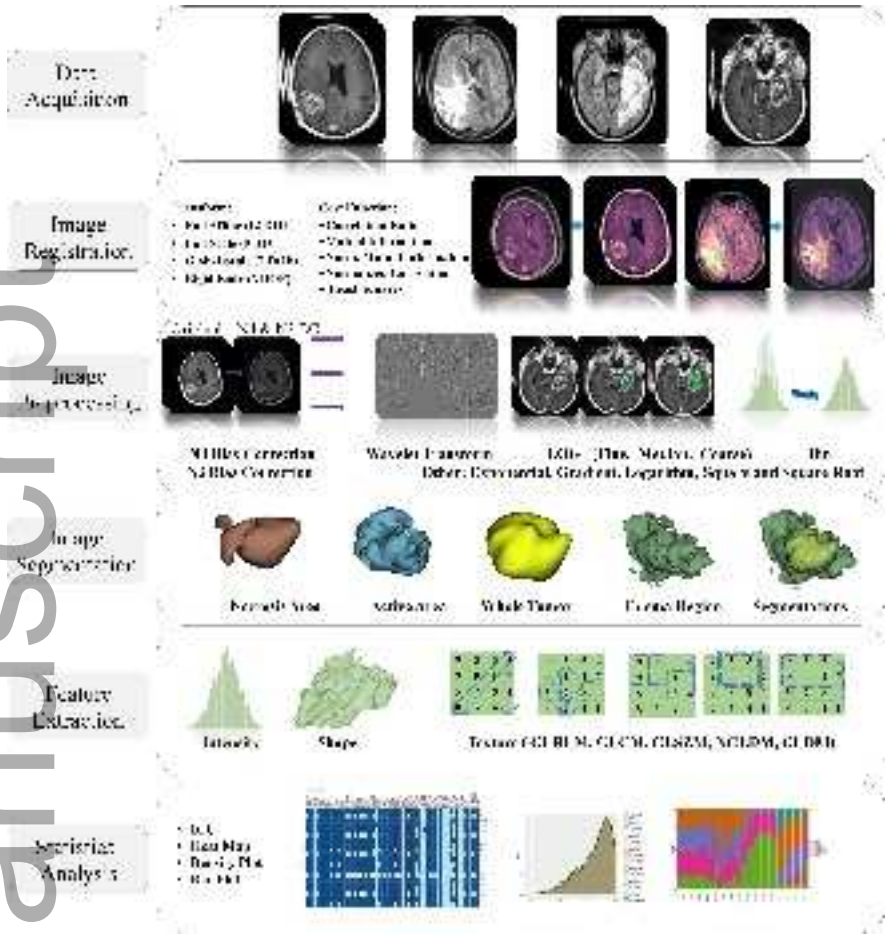
Table 1. Image acquisition and reconstruction parameter details.

Images	Magnet	TE, TR	Resolution	Flip Angle
Contrast-enhanced 3D FLASH	1.5 T	TR: 8.6 ms TE: 4.1 ms	256 x 256 1mm isotropic	20 degree
T2-weighted 3D FLAIR	1.5 T	TR: 6000 ms TE: 353 ms TI: 2200 ms	256 x 256 1mm isotropic	180 degree

Table 2. Highly repeatable features (ICC ≥ 0.95) against different registration settings in N4 bias corrected images.

Registration	FA_CR	FS_CR	GS_CR	RB_CR	FA_LS	FS_LS	GS_LS	RB_LS	FA_MI	FS_MI	GS_MI	RB_MI	FA_NC	FS_NC	GS_NC	RB_NC	FA_NMI	FS_NMI	GS_NMI	RB_NMI
FBC (16)	21.5	14	10.8	14	14	14	9.68	15.1	**26.9**	19.4	11.8	15.1	14	14	10.8	14	19.4	18.3	14	18.3
FBC (32)	19.4	15.1	11.8	15.1	16.1	16.1	9.68	15.1	**24.7**	19.4	12.9	18.3	16.1	16.1	11.8	15.1	21.5	19.4	15.1	20.4
FBC (64)	21.5	16.1	12.9	12.9	15.1	15.1	9.68	14	**25.8**	19.4	14	15.1	17.2	15.1	12.9	16.1	20.4	21.5	16.1	19.4
FBC (128)	18.3	12.9	11.8	14	15.1	14	11.8	14	**21.5**	17.2	12.9	11.8	14	12.9	11.8	14	17.2	17.2	15.1	16.1
FBC (256)	23.7	20.4	11.8	19.4	18.3	19.4	11.8	20.4	**28**	20.4	12.9	14	19.4	20.4	11.8	20.4	21.5	20.4	15.1	19.4
FBW (16)	21.5	17.2	16.1	18.3	17.2	17.2	15.1	17.2	**25.8**	22.6	17.2	17.2	18.3	18.3	16.1	17.2	22.6	22.6	20.4	20.4
FBW (32)	21.5	16.1	16.1	17.2	16.1	16.1	15.1	16.1	**23.7**	20.4	17.2	17.2	17.2	17.2	16.1	17.2	20.4	20.4	19.4	18.3
FBW (64)	18.3	12.9	12.9	12.9	12.9	12.9	11.8	12.9	**20.4**	16.1	15.1	15.1	12.9	12.9	12.9	12.9	16.1	15.1	16.1	16.1
FBW (128)	15.1	9.68	9.68	9.68	9.68	9.68	8.6	9.68	**17.2**	12.9	10.8	11.8	9.68	9.68	9.68	9.68	12.9	12.9	12.9	11.8
FBW (256)	30.1	26.9	26.9	26.9	25.8	25.8	24.7	25.8	**32.3**	30.1	28	24.7	22.6	23.7	26.9	25.8	30.1	30.1	30.1	28
Exponential	3.23	3.23	1.08	1.08	1.08	2.15	0	2.15	**4.3**	**4.3**	0	1.08	3.23	2.15	1.08	2.15	**4.3**	**4.3**	0	2.15
Gradient	9.68	9.68	7.53	**10.8**	9.68	8.6	3.23	9.68	**10.8**	9.68	7.53	7.53	9.68	9.68	7.53	9.68	**10.8**	9.68	6.45	9.68
Logarithm	14	12.9	7.53	14	12.9	12.9	4.3	12.9	14	11.8	11.8	11.8	11.8	7.53	6.45	**15.1**	12.9	12.9	12.9	14
Square	19.4	10.8	8.6	8.6	9.68	7.53	1.08	6.45	**24.7**	17.2	9.68	7.53	10.8	10.8	8.6	8.6	17.2	14	9.68	14
Square Root	19.4	18.3	11.8	15.1	16.1	16.1	10.8	15.1	**24.7**	19.4	14	17.2	16.1	15.1	11.8	14	17.2	16.1	14	22.6
LOG (S=0.5mm)	8.6	9.68	4.3	9.68	9.68	9.68	5.38	9.68	**10.8**	**10.8**	4.3	7.53	8.6	8.6	4.3	8.6	9.68	9.68	5.38	9.68
LOG (S=1.0mm)	41.9	33.3	17.2	35.5	32.3	34.4	6.45	32.3	**49.5**	36.6	21.5	21.5	34.4	33.3	18.3	35.5	36.6	36.6	21.5	38.7
LOG (S=1.5mm)	60.2	50.5	30.1	47.3	51.6	49.5	14	48.4	**62.4**	53.8	31.2	41.9	50.5	51.6	30.1	50.5	54.8	53.8	33.3	54.8
LOG (S=2.0mm)	64.5	54.8	40.9	54.8	55.9	54.8	24.7	54.8	**66.7**	58.1	43	48.4	55.9	55.9	40.9	55.9	58.1	57	43	60.2
LOG (S=2.5mm)	72	67.7	53.8	67.7	68.8	66.7	28	66.7	**74.2**	72	55.9	63.4	68.8	67.7	53.8	67.7	69.9	72	55.9	71
LOG (S=3.0mm)	77.4	71	55.9	69.9	72	69.9	36.6	71	**79.6**	78.5	59.1	69.9	72	71	55.9	69.9	77.4	78.5	59.1	75.3
LOG (S=3.5mm)	72	69.9	51.6	69.9	74.2	73.1	32.3	68.8	73.1	**77.4**	57	67.7	74.2	68.8	51.6	69.9	**77.4**	76.3	57	76.3
LOG (S=4.0mm)	72	79.6	55.9	78.5	79.6	79.6	31.2	78.5	73.1	**80.6**	59.1	66.7	79.6	**80.6**	55.9	79.6	**80.6**	**80.6**	57	78.5
LOG (S=4.5mm)	72	80.6	50.5	79.6	80.6	**82.8**	31.2	78.5	77.4	**82.8**	51.6	68.8	79.6	81.7	49.5	81.7	**82.8**	**82.8**	51.6	80.6
LOG (S=5.0mm)	66.7	65.6	44.1	64.5	66.7	65.6	30.1	64.5	66.7	68.8	46.2	65.6	68.8	66.7	44.1	66.7	69.9	69.9	46.2	**71**
Wavelet (HHH)	**7.53**	**7.53**	4.3	**7.53**	**7.53**	**7.53**	4.3	6.45	6.45	**7.53**	3.23	6.45	**7.53**	**7.53**	4.3	**7.53**	**7.53**	**7.53**	3.23	5.38
Wavelet (HHL)	7.53	**8.6**	3.23	6.45	6.45	6.45	2.15	6.45	**8.6**	7.53	3.23	7.53	7.53	**8.6**	3.23	6.45	7.53	7.53	3.23	7.53
Wavelet (HLH)	7.53	**8.6**	5.38	**8.6**	7.53	**8.6**	5.38	**8.6**	**8.6**	**8.6**	5.38	**8.6**	7.53	**8.6**	5.38	**8.6**	**8.6**	**8.6**	5.38	**8.6**
Wavelet (HLL)	7.53	7.53	5.38	8.6	7.53	7.53	3.23	7.53	**9.68**	8.6	5.38	7.53	7.53	8.6	6.45	8.6	7.53	7.53	5.38	7.53
Wavelet (LHH)	**10.8**	9.68	5.38	8.6	9.68	9.68	5.38	8.6	9.68	8.6	5.38	8.6	9.68	9.68	6.45	8.6	8.6	8.6	5.38	8.6
Wavelet (LHL)	10.8	10.8	3.23	**11.8**	9.68	9.68	2.15	**11.8**	**11.8**	**11.8**	2.15	**11.8**	9.68	10.8	3.23	10.8	**11.8**	**11.8**	2.15	**11.8**
Wavelet (LLH)	**9.68**	7.53	4.3	8.6	8.6	8.6	3.23	7.53	**9.68**	8.6	3.23	**9.68**	6.45	7.53	3.23	8.6	7.53	8.6	4.3	7.53
Wavelet (LLL)	44.1	38.7	25.8	36.6	38.7	37.6	16.1	35.5	**45.2**	41.9	30.1	37.6	36.6	35.5	24.7	37.6	44.1	40.9	30.1	44.1

*FBC: Fixed Bin Count, FBW: Fixed Bin Width, LOG: Laplacian of Gaussian, S: Sigma



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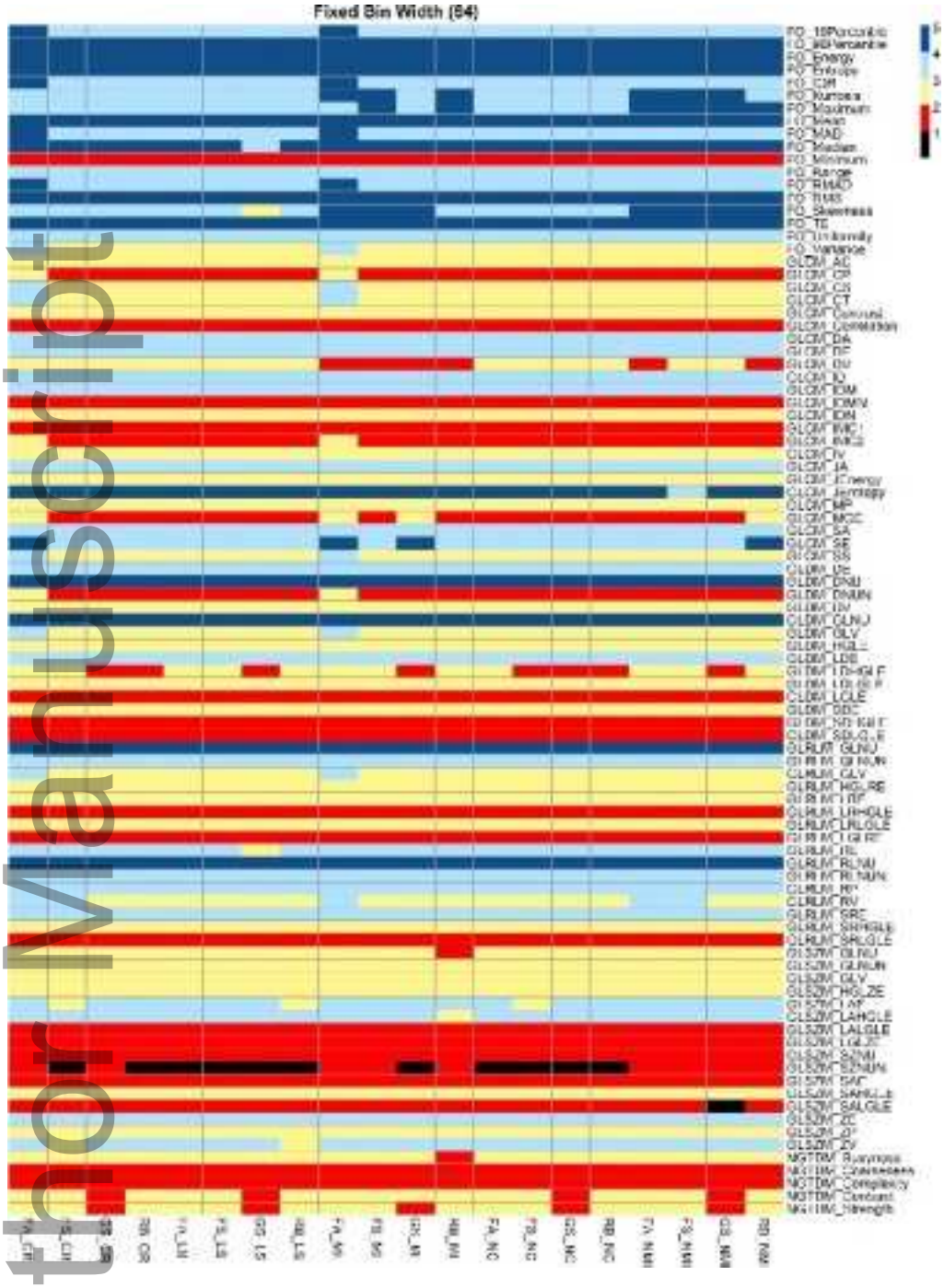

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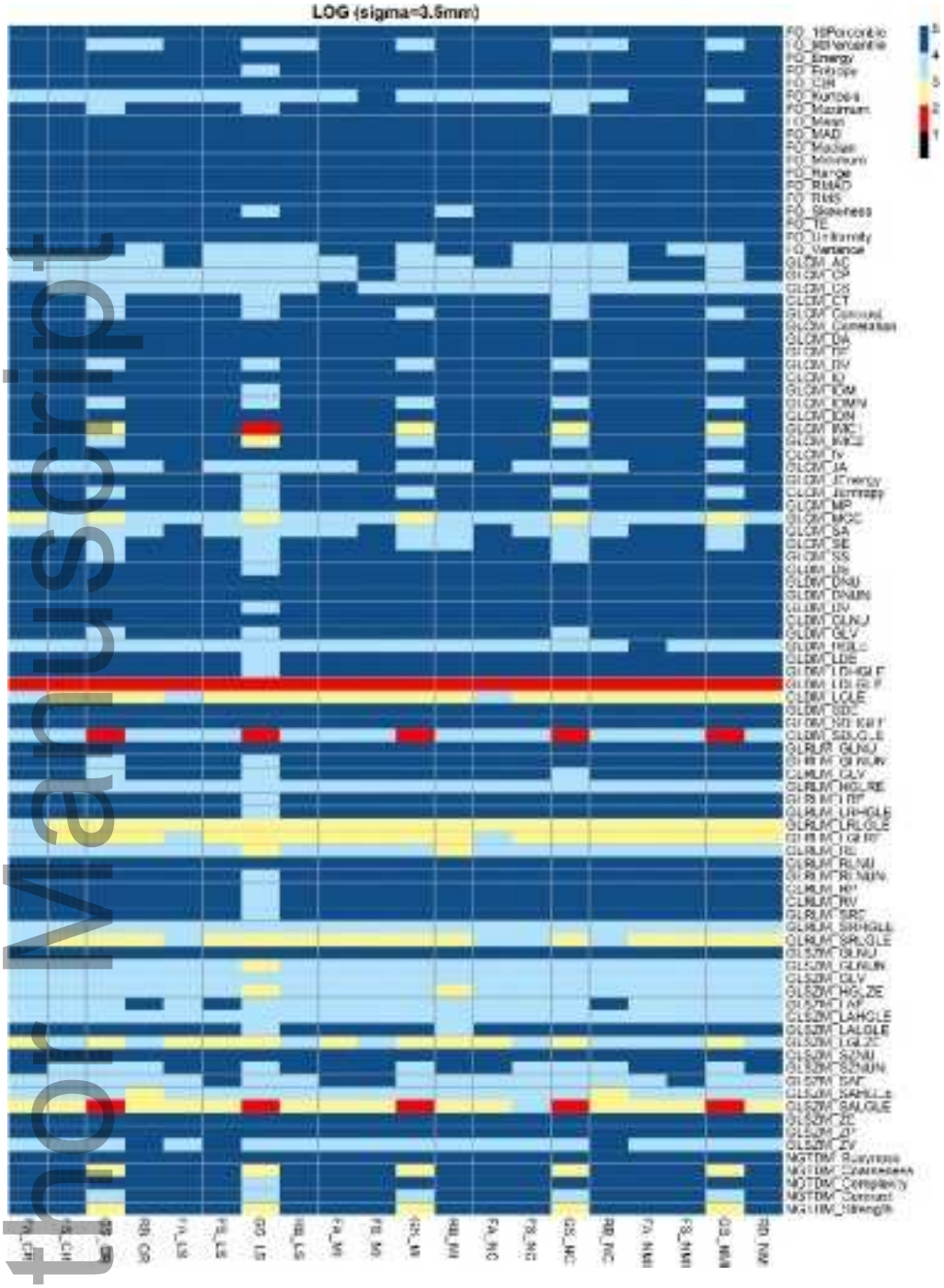

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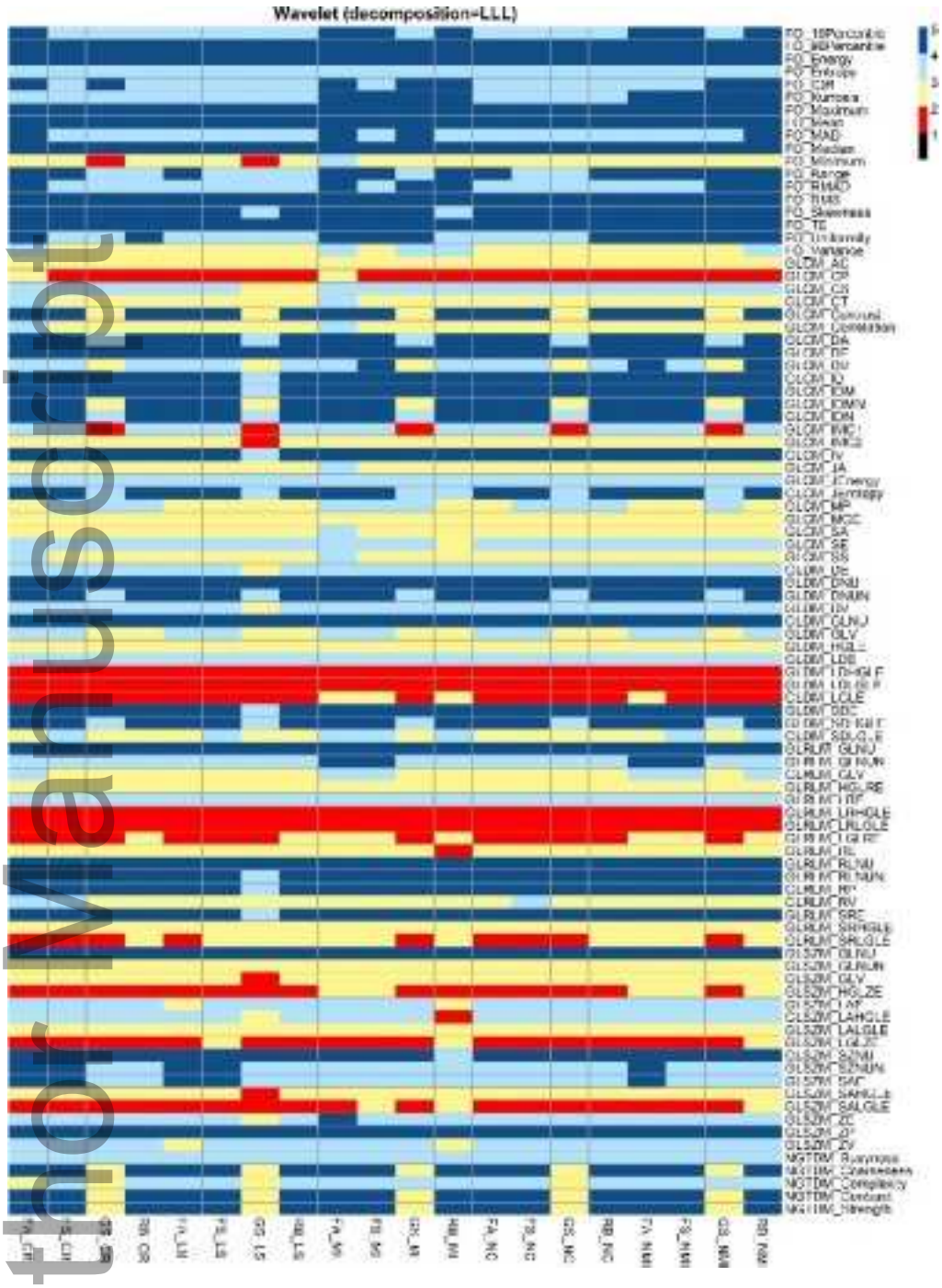

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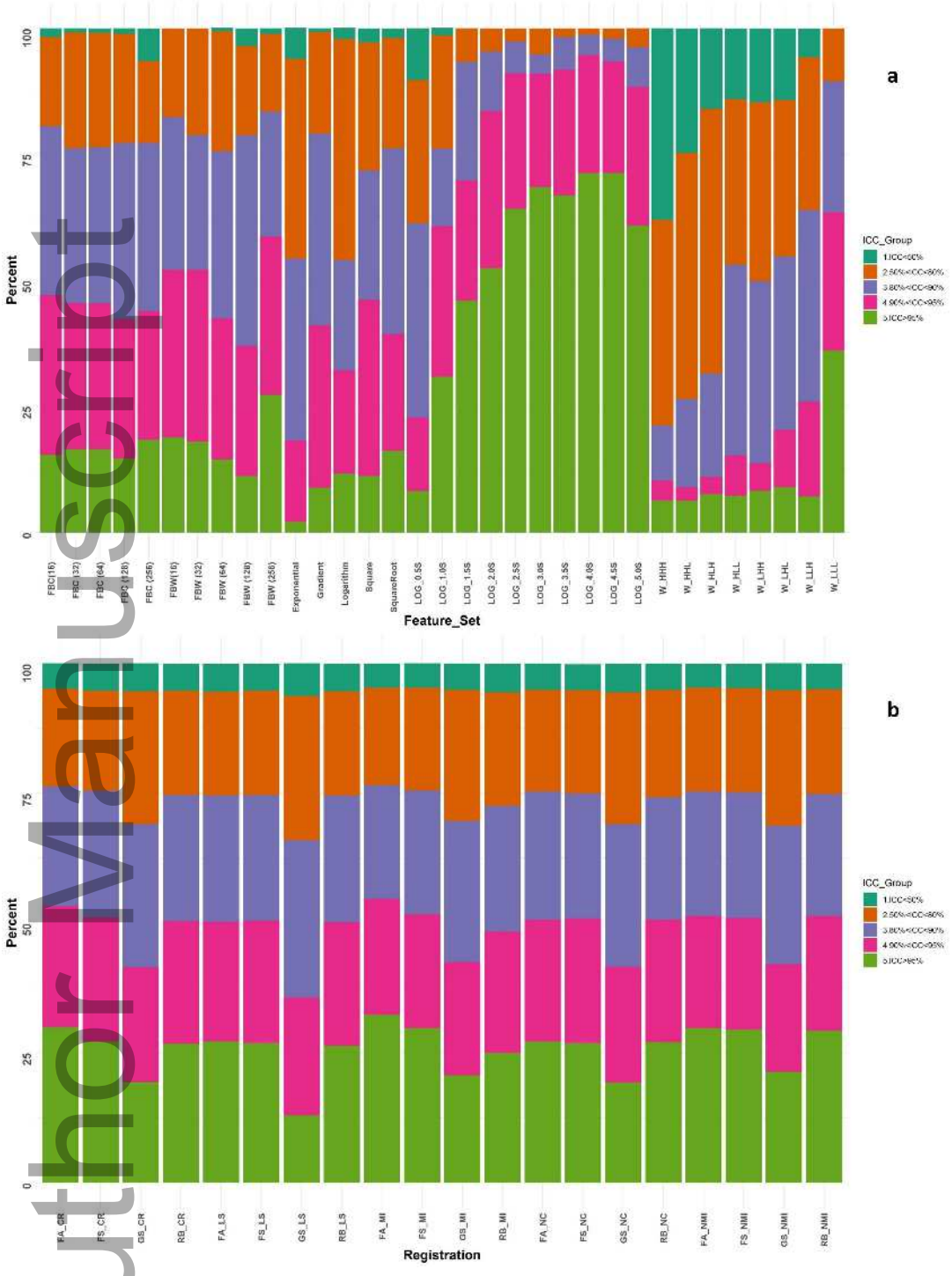

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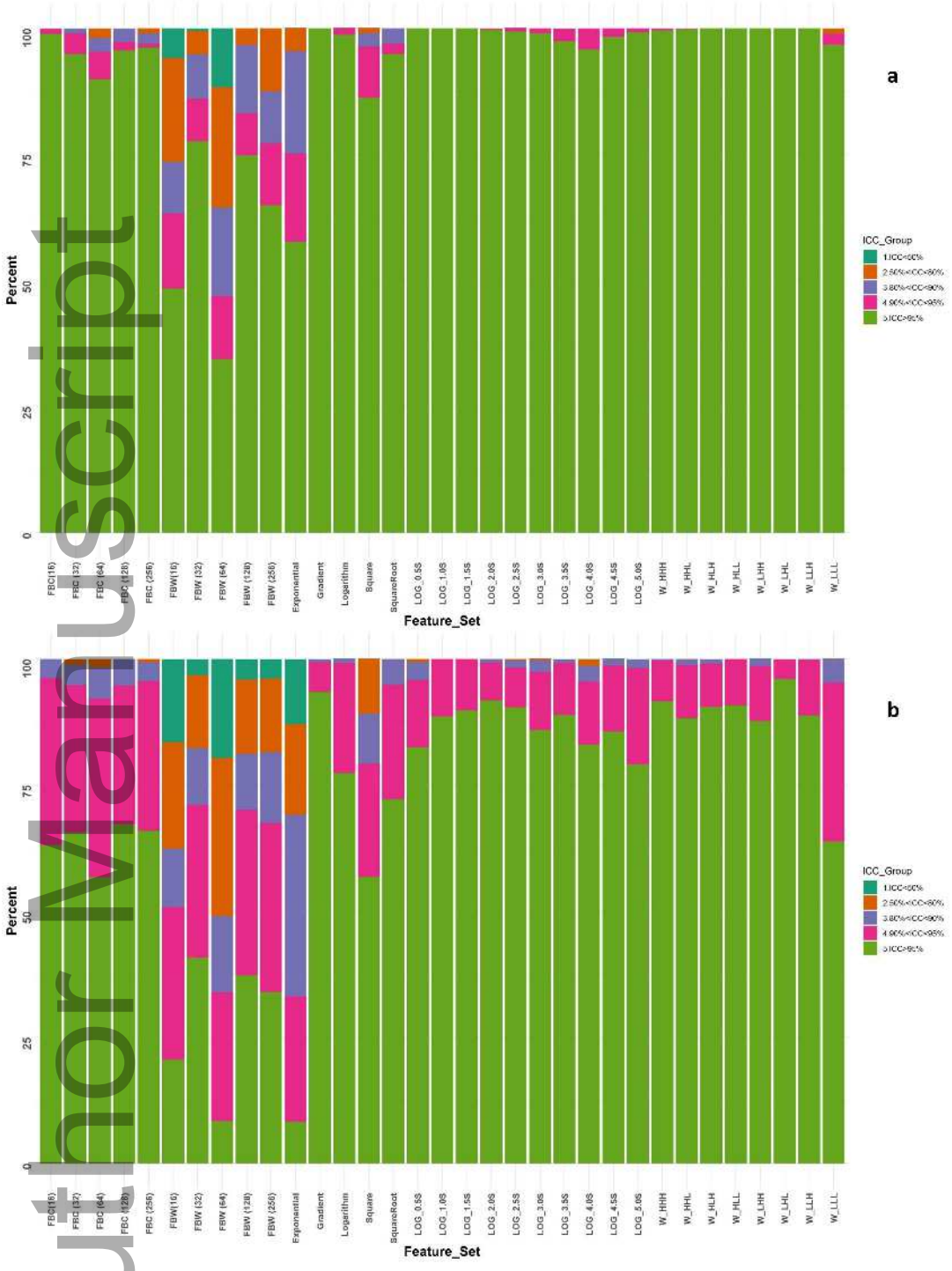

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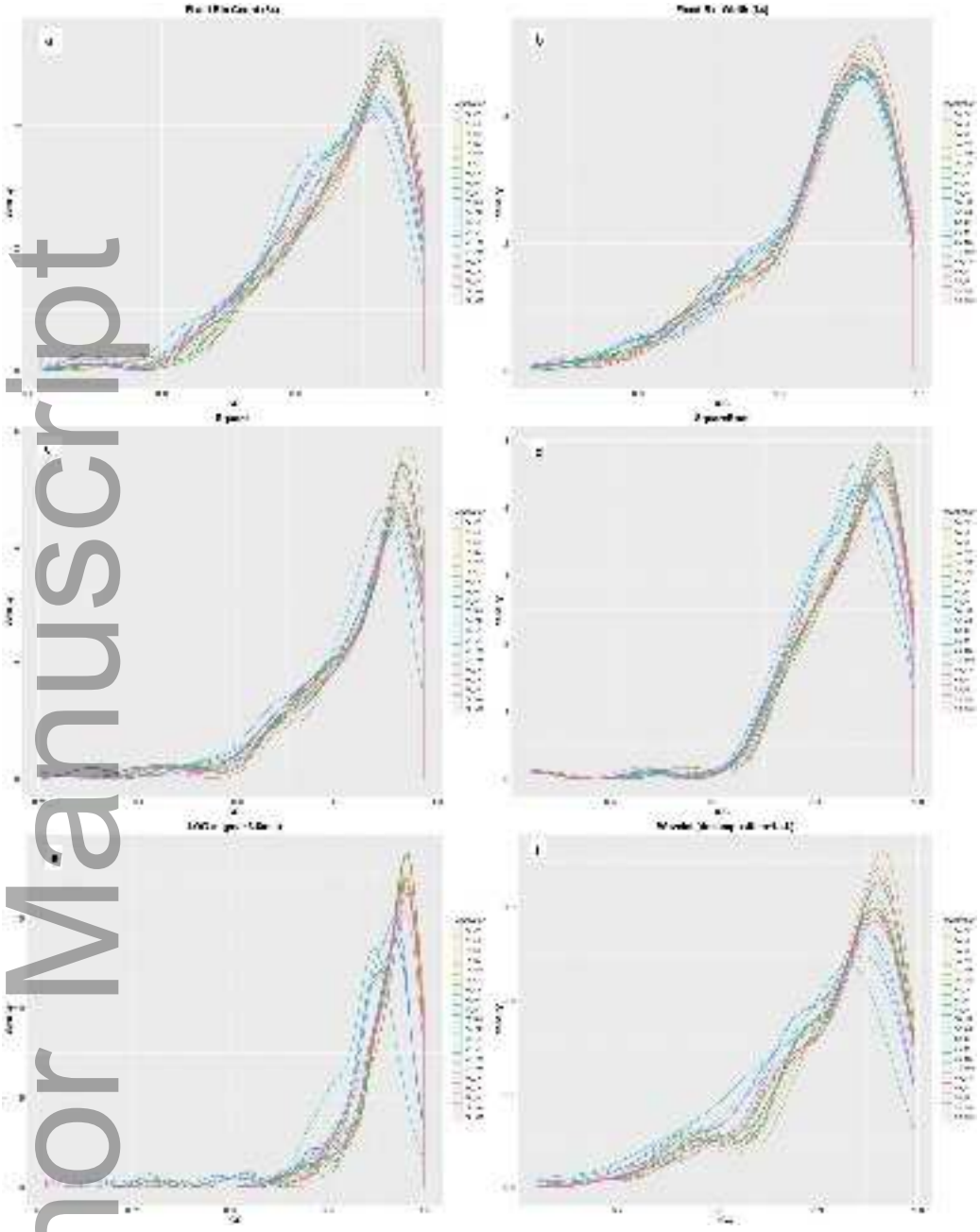

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