Published in final edited form as:

Magn Reson Imaging. 2018 February ; 46: 21–27. doi:10.1016/j.mri.2017.10.003.

Model Selection for High b-value Diffusion-weighted MRI of the Prostate

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Abstract

Purpose—To assess the abilities of the standard mono-exponential (ME), bi-exponential (BE), diffusion kurtosis (DK) and stretched exponential (SE) models to characterize diffusion signal in malignant and prostatic tissues and determine which of the four models best characterizes these tissues on a per-voxel basis.

Materials and Methods—This institutional-review-board-approved, HIPAA-compliant, retrospective study included 55 patients (median age, 61 years; range, 42–77 years) with untreated, biopsy-proven PCa who underwent endorectal coil MRI at 3-Tesla, diffusion-weighted MRI acquired at eight b-values from 0 to 2000 s/mm². Estimated parameters were apparent diffusion coefficient (ME model); diffusion coefficients for the fast (D_{fast}) and slow (D_{slow}) components and fraction of fast component, f_{fast} (BE model); diffusion coefficient D , and kurtosis K (DK model); distributed diffusion coefficient DDC and α for (SE model). For one region-of-interest (ROI) in PZ and another in PCa in each patient, the corrected Akaike information criterion (AICc) and the Akaike weight (w) were calculated for each voxel.

Results—Based on AICc and w , all non-monoexponential models outperformed the ME model in PZ and PCa. The DK model in PZ and SE model in PCa ROIs best fit the greatest average percentages of voxels (39% and 43%, respectively) and had the highest mean w ($35 \pm 16 \times 10^{-2}$ and $41 \pm 22 \times 10^{-2}$, respectively).

Conclusion—DK and SE models best fit DWI data in PZ and PCa, and non-ME models consistently outperformed the ME model. Voxel-wise mapping of the preferential model demonstrated that the vast majority of voxels in either tissue type were best fit with one of the non-monoexponential models. At the given SNR levels, the maximum b-value of 2000 s/mm² is not sufficiently high to identify the preferred non-monoexponential model.

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Keywords

diffusion-weighted MRI (DW-MRI); prostate cancer (PCa); mono-exponential model (ME); bi-exponential model (BE); diffusion kurtosis (DK); stretched exponential (SE)

INTRODUCTION

Diffusion-weighted (DW) magnetic resonance imaging (MRI) has become an increasingly important component of clinical evaluation of the prostate for detection and characterization of prostate cancer (PCa). The standard model for water diffusion within the prostate is that of monoexponential water diffusion; this model estimates the apparent diffusion coefficient (ADC) of free water diffusion and has shown potential for assisting in prostate cancer detection and characterization when combined with anatomical imaging for tumor localization [1–3]. Commonly, two or more DW images are acquired, with one low b-value (often 0 s/mm²) and the remaining b-values extending up to 1000 s/mm²; these images are fitted to a monoexponential model to calculate ADC values, which can then be displayed as ADC parametric maps.

A number of studies have investigated deviations of diffusion signal from monoexponential (ME) behavior using high-b-value DWI (typically considered to be DWI with a b-value range up to or beyond 2000 s/mm²) [4–8]. Models considered for the analysis of high-b-value prostate data include the bi-exponential (BE) model, in which the relative contributions from “fast” and “slow” components of the signal decay are quantified; diffusion kurtosis (DK) imaging [6, 7], which estimates the diffusion coefficient as well as the kurtosis, a metric for the degree of non-Gaussian behavior [9]; and the stretched exponential (SE) formalism, which, similarly to DK imaging, makes no assumption as to the tissue compartmentalization but, rather, uses a stretching parameter to measure heterogeneity of the environment [8, 10].

Such complex parametric models are increasingly being used to describe diffusion characteristics of malignant and prostate tissues, and efforts are being made to assess how well they fit diffusion characteristics in these tissues. As the ‘true’ diffusion model is unavailable for human in-vivo studies, evaluation of the models is based on a statistical approach that was used by Wittsack [11] to evaluate DWI of the human kidney and has since been extended to DWI of the prostate [12–14] and other organs, such as the breast [15, 16].

The purpose of our study was to assess the abilities of the ME, BE, DK, and SE models to characterize diffusion signal in malignant and prostatic tissues and determine which of the four models best characterizes these tissues on a per-voxel basis.

THEORY

Mathematical Models for Diffusion

Standard monoexponential model of diffusion—In the simplest case, the diffusion decay is described by a ME model:

$$S(b) = S(0) \cdot \exp(-b \cdot \text{ADC}) \quad [1]$$

where $S(b)$ and $S(0)$ are signal intensities of each voxel with and without diffusion weighting, the quantity b is the diffusion-sensitizing factor (commonly referred to as the b -value), and ADC is the apparent diffusion coefficient.

Bi-exponential (BE) model of diffusion—The BE signal decay equation provides a four-parameter model of signal as follows [4, 5]:

$$S(b) = S(0) \cdot [f_{\text{fast}} \cdot \exp(-b \cdot D_{\text{fast}}) + (1 - f_{\text{fast}}) \cdot \exp(-b \cdot D_{\text{slow}})] \quad [2].$$

In this model, the signal decay is assumed to be due to two components: the fast component with diffusion coefficient D_{fast} and fraction of f_{fast} , and the slow component with diffusion coefficient D_{slow} and fraction $(1 - f_{\text{fast}})$.

Diffusion Kurtosis (DK) Imaging—The DK model provides a three-parameter signal decay equation given by [9]:

$$S(b) = S(0) \cdot \left[\exp(-b \cdot D + b^2 \cdot K \cdot D^2/6) \right] \quad [3]$$

where D is the diffusion coefficient adjusted for non-Gaussian behavior, and K is the diffusion kurtosis, which quantifies non-Gaussian diffusion. K is a dimensionless statistical metric that quantifies the non-Gaussian behavior of an arbitrary probability distribution. When $K=0$, the standard ME model is recovered. Due to the complex histology of cancer cells in PCa, it has been suggested that the DK model could provide better characterization of prostate cancer than the standard ME model [6, 7].

Stretched Exponential (SE) Model—The SE model allows gauging in a simple way the deviations from the monoexponential model through a three-parameter SE signal decay equation:

$$S(b) = S(0) \cdot \exp\{-(b \cdot \text{DDC})^\alpha\} \quad [4]$$

where DDC is the distributed diffusion coefficient. Alpha (α) is a dimensionless parameter with a value between 0 and 1; it characterizes deviation of the signal attenuation from monoexponential form and is used to measure heterogeneity of the environment. The stretched exponential model assumes a continuous distribution of diffusion coefficients where represents deviation from monoexponential decay.

Model Selection

The Akaike's Information Criterion (AIC) is often used to identify the model that best fits data. AIC estimates the goodness-of-fit while incorporating the number of model parameters and is given by [11]:

$$AIC = N \cdot \ln(SS) + 2p \quad [5]$$

where N is the number of data points, SS the sum of squared deviance, and p the number of estimated parameters. Typically, when sample sizes are small compared to the number of parameters ($N/p < 40$), AIC corrected for finite sample sizes (AICc) is used:

$$AICc = AIC + \frac{2p \cdot (p + 1)}{N - p - 1} \quad [6]$$

When multiple models are compared using the same data set, the model with the lowest AICc is considered the preferred model.

After the AICc is determined for each model i , further comparison can be achieved by determining the quantity delta AICc _{i} (or Δ_i), which is given by [17]:

$$\Delta_i = AICc_i - \min(AICc) \quad [7]$$

Δ_i is estimated by measuring the difference between the AICc for any given model i and the AICc for the best model, which would have the lowest AICc. Thus, the best of the models being compared would have a delta AICc of zero.

The Akaike weight (w_i) represents the relative ratio of $\exp(-\Delta_i/2)$ for each model to the value for all potential candidate models [17]:

$$w_i = \frac{\exp(-\Delta_i/2)}{\sum_{r=1}^R \exp(-\Delta_r/2)} \quad [8]$$

where R is the total number of candidate models. The Akaike weight for each model represents the probability that the model is the best among the selection of models.

MATERIALS AND METHODS

Patients

This retrospective study was compliant with the Health Insurance Portability and Accountability Act and was approved by our institutional review board, which waived the requirement for written informed consent. The study included 55 patients (median age, 61 years; range, 42–77 years) with untreated, biopsy-proven prostate cancer, who were referred

for MRI of the prostate between October 2012 and February 2013 and whose MRI examination included DW-MRI.

MRI Data Acquisition

MR imaging was performed with a 3-T whole-body MRI unit (Discovery MR750; GE Medical Systems, Waukesha, WI) equipped with an 8-channel phased-array coil and a commercially available balloon-covered expandable endorectal coil (Medrad, Pittsburgh, PA) for signal reception. The DWI protocol was carried out using a spin-echo echoplanar imaging sequence in the axial plane with the following b-values: 0, 600, 800, 1000, 1200, 1400, 1800, and 2000 s/mm². Other parameters included TR/TE, 3000–4000/78.2–80.4 ms; matrix, 96×96; field of view, 160×160 mm²; resolution, 1.67×1.67×3 mm³; diffusion direction, all three directions; diffusion time, 24.5 ms; and an acceleration factor of 2. Two averages were acquired.

Image Analysis

The acquired datasets were transferred to a personal computer, and data analysis was performed with in-house software. Using ImageJ software (U.S. National Institutes of Health), a radiologist reviewed the T2-weighted images as well as ADC maps and traced suspected tumor areas (ie, regions of interest [ROIs]) that demonstrated focally low signal intensity relative to the high signal intensity of normal PZ. Areas containing post-biopsy changes or prostate capsule, which can result in signal abnormality on diffusion and T2-weighted images, were avoided. T1-weighted images were used to detect post-biopsy changes. For all ROIs, parametric maps of diffusion coefficients and other parameters were generated on a voxel-wise basis using all b-values; a Matlab program (version R2014b, The MathWorks, Inc., Natick, MA, USA) was employed for this purpose. Diffusion-attenuated signal intensities within ROIs were fitted against b-values according to the four diffusion models, using the non-linear least-squares fitting based on the Levenberg-Marquardt algorithm. This algorithm simultaneously determines the values of all parameters in each voxel by a least-squares fit [18]. The starting point was constant for all voxels and initialized based on literature values for each parameter. For each model, an estimate of the signal intensity at b=0 ($S(0)$) was also obtained.

For each voxel, the model with the lowest AICc value was identified. In addition, the delta AICc ($\Delta AICc_i$) and Akaike weight (w_i) were calculated for each model in each voxel. Summary statistics for the parameters of each model, as well as the percentage of voxels for which each model was preferred, were calculated. The Wilcoxon rank-sum test was used to test for statistically significant differences among the Akaike weights and to compare model parameters in PZ and PCa ROIs. P-values less than 0.05 were considered to indicate statistically significant difference.

RESULTS

Examples of mono-exponential, bi-exponential, diffusion kurtosis, and stretched exponential curves fitted to the data from one voxel in PZ tissue and one voxel in PCa are shown in Figure 1. The mean and standard deviation values of parameters derived from the four

models are provided in Table 1. ADC parameter derived from the ME model, D_{slow} and f_{fast} parameters derived from the BE model, D_K and K parameters derived from the DK model, and DDC and α parameters derived from the SE model were significantly different in PCa as compared to PZ ($p < 0.001$). D_{fast} derived from the BE model was not significantly different in PCa as compared to PZ ($p = 0.33$) (Figure 2).

Figure 3 shows parametric maps generated from each model for a slice from a single patient, along with the corresponding T2-weighted image. Figure 4 shows representative spatial maps of a PZ ROI and a PCa ROI, where each voxel is labeled with the model that attained the lowest AICc. Also shown are images at $b = 0, 1000$, and 2000 s/mm^2 . In PZ ROIs, the DK model had the lowest mean AICc and the highest mean Akaike weight, while the ME model had the highest mean AICc and the lowest mean Akaike weight (Table 2). In PCa ROIs, the SE model had the lowest AICc and the highest Akaike weight, while the ME model again had the highest mean AICc and the lowest mean Akaike weight (Table 2).

In the ROIs obtained from PZ, 39% of voxels were best fitted by the DK model, 30% by the SE model, 28% by the BE model, and 3% by the ME model. No PZ regions had a majority of voxels best fitted by the ME model, as compared to 24/54 for the BE model. In PCa ROIs, 43% of voxels were best fitted by the SE model, 29% by the BE model, 26% by the DK model, and 2% by the ME model. No PCa regions had a majority of voxels best fitted by the ME model, as compared to 29/54 with a majority best fitted by the SE model (Table 3).

Comparisons of the Akaike weights for pairs of models are summarized in Table 4. Figure 5 shows representative spatial maps of delta AICc and w for a PCa ROI. Figure 6 shows the spatial map of the preferred model for one of the rare PCa ROIs in which some voxels were best characterized by the ME model.

DISCUSSION

In this work we compared four models commonly used in the analysis of high- b -value DWI of the prostate. Model comparison was based on AICc, delta AICc and Akaike weights for both peripheral zone and prostate cancer. The model with the lowest AICc is considered the preferred model, while the calculated Akaike weights provide a complementary measure of the probability that a model is the best among the selected set. Delta AICc provides a measure of the difference in fit between the best model (that with the lowest AICc) and each of the other models compared.

Wittsack et al. [11] presented one of the first reports on the evaluation of DWI of the kidney, in which they compared ME and BE models and a statistical model for diffusion-attenuated MR signal [19]. Their work has been extended to the prostate by a number of investigators [12–14]. In contrast to most of the prior analyses, our analysis was performed on a voxel-wise basis; in addition, rather than comparing model parameters across tissue types, as was done previously [13], our study was specifically intended to compare how well models fit within each tissue type through both binary analysis (based on minimum AICc) as well as probabilistic analysis (based on Akaike weights). First we estimated (on a voxel-wise basis)

the mean AICc for each region and determined which model had the overall lowest AICc (Table 2). Second, we measured delta AICc and the Akaike weights.

In the analysis by Jambor et al., the BE model had the lowest AICc [14]. Given that our estimates of AICc were based on a voxel-wise analysis and hence more sensitive to noise, it was to be expected that our AICc values would be closer to the tail-end of the simulation plot of Jambor et al., which presents delta AICc as a function of increasing noise standard deviation (Figure 5, Ref. [14]); at this end of the noise level the differences in delta AICc in that plot are negligible, which is consistent with our findings.

Models that have larger numbers of parameters tend to over-fit the data, whereas simple models with few parameters do not capture the full system information available in the measurements. The corrected AIC (AICc) is a measure of information loss by a particular model, which incorporates both the goodness-of-fit and the number of parameters and therefore discourages over-fitting. A lower AICc implies less information loss by a model, without the need for a cutoff entailed by an F-test [12]. Our analysis showed that for PZ, the DK model had the lowest mean AICc, while for prostate cancer, the SE model had the lowest mean AICc. However, the comparison between non-monoexponential models suggests only a modest variation among different models within tissue (both PZ and PCa). The DK model was the preferred model for, on average, 39.02% of PZ voxels, and the SE model was the preferred model for, on average, 42.54% of PCa voxels. None of the models compared could optimally characterize the majority of voxels within a tissue type. In PZ, the model that fit the largest number of voxels in the largest number of ROIs (the BE model), was different from the model that had the lowest AICc and highest Akaike weight (the DK model).

When models were compared based on mean Akaike weights, all non-monoexponential models (BE, SE, DK) were significantly superior to the ME model in both PZ and PCa. However as the spatial maps (Figures 4, 6) suggest, no single non-monoexponential model best characterized all voxels although the vast majority of the voxels were best fit with one of the non-monoexponential models. Although the spatial maps provide an overall display of the preferred model, their interpretability is limited by image quality, distortion, noise, and low spatial resolution.

Our study had several limitations. First, our analysis of high-b-value DWI data did not incorporate Rician noise distributions, which can result in bias in the estimation of model parameters in high-b-value (low signal-to-noise (SNR)) DWI [20]. In the future, we will examine the models while incorporating the SNR through the maximum likelihood estimation methods discussed in the literature. Second, we did not examine the source of non-monoexponential diffusion signal decay. Although the origins of non-monoexponential decay in tissue (brain, brain tumor, prostate) are not fully understood, experimental results suggest that two distinct water compartments result in a diffusion signal decay which is best characterized by a BE model [4]. Bourne et al. have suggested that the distinct stromal and epithelial diffusion compartments are potentially the likely origin of BE diffusion decay observed in vivo [21]. In our study, the non-monoexponential models were clearly preferable to the ME model while the differences among non-monoexponential models were not

distinctively different. Third, we used eight b-values, but the appropriate number of b-values and the upper limit of b-values for DWI studies involving the prostate have not been established. We postulate that while a maximum b-value of 2000 s/mm² clearly demonstrates that non-monoexponential signal models are preferable to the monoexponential model; this maximum b-value is not sufficiently high to identify the preferred non-monoexponential model. Fourth, we did not evaluate our models in terms of detection and characterization of prostate cancer. Toivonen et al. recently performed an ROI-based analysis comparing the four models and concluded that the monoexponential model was sufficient for PCa detection and characterization [22]. In contrast, our analysis revealed a voxel-wise mapping of the preferential model. Fifth, we did not account for perfusion effects. The inclusion of b=0 could have introduced an error in the estimation of D_{fast} , since the perfusion component was not considered in the fit. Finally, in our study, a single radiologist outlined the ROIs with awareness of the location of cancerous sextants at biopsy but without reference to histopathological slides. As the aim of our study was to compare alternative models for each tissue type rather than to perform a clinical evaluation of diagnostic performance, we considered the available clinical information to be sufficient.

In summary, based on comparison of AICc and Akaike weights, the diffusion kurtosis model provided the best fit to DWI data from PZ measurements, whereas the stretched exponential model provided the best fit to DWI data from PCa measurements. However, no model provided the best fit for a majority of voxels in either tissue type. Voxel-wise mapping of the preferential model demonstrated that the vast majority of voxels was best fitted with non-monoexponential models, whereby none of the three non-monoexponential models were clearly preferred over the other two.

Acknowledgments

We are grateful to Ada Muellner, M.S. for helping to edit this manuscript.

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Figure 1. Normalized plots of the measured DWI signals vs. b-values and the best-fit curves from a voxel within (A) PZ, and (B) PCa. The data is fitted to four models: monoexponential (green), bi-exponential (yellow), diffusion kurtosis (red), stretched exponential (blue).

Figure 2.

Box-and-whisker plot of parametric maps derived from each model in prostate cancer (PCa) and benign PZ ROIs from 55 patients. On each box, the central mark indicates the median parameter value, and the bottom and top edges of the box indicate the 25th and 75th percentiles, respectively.

Figures 3.

Transverse parametric maps of the prostate from a 69-year-old patient with tumor located in the PZ (presurgical PSA level, 5.01 ng/mL; biopsy Gleason score, 7 [4+3]). (A)–(D) Parametric maps derived from each model. (A) For the ME model, the ADC map is shown. (B) From the DK model, diffusion coefficient D , and kurtosis K are shown. (C) From the BE model, diffusion coefficients for the fast (D_{fast}) and slow (D_{slow}) components and fraction of fast component, f_{fast} , are shown. (D) From the SE model, distributed diffusion coefficient DDC and α are shown. (E) Transverse T2-weighted image from the same location.

Figures 4.

(A) A transverse T2-weighted MR image of the peripheral zone of the prostate from a 64-year-old patient with tumor located in the PZ (presurgical PSA level, 4.7 ng/mL; biopsy Gleason score, 7 [3+4]). (B) A map showing the model selection for the PCa ROI (red) in (A), where each voxel is identified with the preferred model (lowest AICc). (C) A map showing the model selection for the PZ ROI (green) in (A) where each voxel is identified with the preferred model (lowest AICc). (D)–(F) Images at $b=0$, 1000, and 2000 s/mm^2 . There is substantial signal attenuation at $b=2000 \text{ s/mm}^2$. Color maps were generated on the basis of voxel-wise calculation using 96×96 acquisition matrix interpolated to 256×256 .

Figure 5.

(A) A transverse T2-weighted MR image of the peripheral zone of the prostate from a 52-year-old patient with tumor located in the PZ (presurgical PSA level, 6.1 ng/mL; biopsy Gleason score, 7 [4+3]). (B) Top row: For the PZ ROI (green), a map of delta AICc (estimated by measuring the difference between the AICc for each model and the AICc for the best model). For each voxel, the model with zero delta AICc is the preferred model. Bottom row: The Akaike weight maps for all models. The Akaike weight values (range, 0–1) represent the probability that the model is considered the best among the selected set. (C) Same as (B) but for PCa ROI (red). Color maps were generated on the basis of voxel-wise calculation using 96×96 acquisition matrix interpolated to 256×256.

Figure 6.

(A) A transverse T2-weighted MR image of the peripheral zone of the prostate from a 62-year-old patient with tumor located in the PZ (presurgical PSA level, 5.2 ng/mL; biopsy Gleason score, 7 [3+4]). (B) A map showing the model selection for the PCa ROI (red) in (A), where each voxel is identified with the preferred model (lowest AICc). Color maps were generated on the basis of voxel-wise calculation using 96×96 acquisition matrix interpolated to 256×256 .

Table 1:

Mean ($\pm$ standard deviation) values of parameters derived from the four models. Also shown are the p-values for how well each parameter of each model differentiates PCa from PZ.

Model Parameters	Peripheral Zone	Prostate Cancer	PZ vs. PCa P-value
ADC ($\mu\text{m}^2/\text{ms}$)	1.65 $\pm$ 0.21	1.04 $\pm$ 0.17	<0.001
D_{fast} ($\mu\text{m}^2/\text{ms}$)	3.02 $\pm$ 0.61	2.95 $\pm$ 0.71	0.33
D_{slow} ($\mu\text{m}^2/\text{ms}$)	0.62 $\pm$ 0.24	0.45 $\pm$ 0.16	<0.001
f_{fast}	0.72 $\pm$ 0.13	0.48 $\pm$ 0.14	<0.001
D_K ($\mu\text{m}^2/\text{ms}$)	2.08 $\pm$ 0.25	1.42 $\pm$ 0.23	<0.001
K	0.64 $\pm$ 0.10	0.93 $\pm$ 0.14	<0.001
DDC ($\mu\text{m}^2/\text{ms}$)	1.83 $\pm$ 0.26	1.15 $\pm$ 0.22	<0.001
α	0.79 $\pm$ 0.06	0.74 $\pm$ 0.06	<0.001

Table 2:

Mean values of AICc and Akaike weight (w) values for the four models, from voxel-wise measurements of all PZ (thought to be benign) and PCa ROIs.

AICc, w	Peripheral Zone	Prostate Cancer
AICc _{ME}	132±10	126±6
AICc _{BE}	115±12	111±8
AICc _{DK}	114±12	112±8
AICc _{SE}	117±10	110±7
$w_{ME} (\times 10^{-2})$	1±6	1±3
$w_{BE} (\times 10^{-2})$	34±15	33±13
$w_{DK} (\times 10^{-2})$	35±16	25±16
$w_{SE} (\times 10^{-2})$	30±22	41±22

Table 3:

Summary of average percentages of voxels within ROIs for which each model provided the best fit (had the lowest AICc). Also included for each model are the numbers of ROIs for which that model was the one that best fit the largest number of voxels.

Model	Peripheral Zone		Prostate Cancer	
	Average % voxels	No of ROIs	Average % voxels	No of ROIs
ME	3%	0/54	2%	0/54
BE	28%	24/54	29%	15/54
DK	39%	12/54	26%	10/54
SE	30%	18/54	43%	29/54

Table 4:

Comparison of mean Akaike weights from PZ (thought to be benign) and PCa ROIs between models.

Model 1 vs Model 2	Peripheral Zone			Prostate Cancer		
	$w_{\text{Model 1}}$	$w_{\text{Model 2}}$		$w_{\text{Model 1}}$	$w_{\text{Model 2}}$	
BE vs. ME	0.96±0.10	0.04±0.10	<0.001*	0.95±0.10	0.05±0.10	<0.001*
DK vs. ME	0.97±0.10	0.03±0.10	<0.001*	0.95±0.09	0.05±0.09	<0.001*
SE vs. ME	0.97±0.11	0.03±0.11	<0.001*	0.93±0.14	0.07±0.14	<0.001*
BE vs. DK	0.51±0.16	0.49±0.16	0.71	0.59±0.18	0.40±0.18	0.025*
BE vs. SE	0.58±0.26	0.42±0.26	0.002*	0.48±0.22	0.52±0.22	0.26
DK vs. SE	0.56±0.28	0.44±0.28	0.03*	0.39±0.27	0.61±0.27	<0.001*

The asterisk indicates significance (Wilcoxon rank-sum test P-value < 0.05).