Semi-automatic quantitative analysis of the pelvic bony structures on apparent diffusion coefficient maps based on deep learning: establishment of reference ranges

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Background: Apparent diffusion coefficient (ADC) maps provide quantitative information on both normal and abnormal tissues. However, it is difficult to distinguish between these tissues unless consistent and precise ADC values can be obtained from normal tissues. For this study we developed a deep learning-based convolutional neural network (CNN) for pelvic bony structure segmentation and established the reference ranges of ADC parameters for normal pelvic bony structures.

Methods: We retrospectively enrolled 767 prostate cancer (PCa) patients for quantitative ADC analyses of normal pelvic bony structures. A subset of 288 patients who did not receive treatment for PCa (S1) were used to develop a CNN model for the segmentation of 8 pelvic bony structures (lumbar vertebra, sacrococcyx, ilium, acetabulum, femoral head, femoral neck, ischium, and pubis). The proposed CNN was used for the automated segmentation of these pelvic bony structures from a subset of 405 patients who did not receive treatment (S2) and 74 patients who received treatment [radiotherapy (S3) or endocrine therapy (S4)]. The 95% confidence interval (CI) was used to establish reference ranges for the ADC values from the normal pelvic bony structures of S1 and S2.

Results: The Dice scores (Sørensen-Dice coefficient) for the CNN segmentation of the 8 pelvic bones on the ADC maps ranged from 0.90±0.02 (ilium) to 0.95±0.03 (femoral head) in the S1 testing set. In the S2 data set, the Dice scores showed no significant difference among the different scanners (P>0.05), and no significant differences were found among the S2, S3, and S4 data sets. The correlation analysis revealed that the b value and field strength were significantly correlated with ADC values (all P<0.001), while age and treatment were not significant variables (all P>0.05). The ADC reference ranges (95% CI) were as follows: lumbar vertebra, 1.11 (0.90–1.54); sacrococcyx, 0.82 (0.61–1.15); ilium, 0.57 (0.45–0.62); acetabulum, 0.59 (0.40–0.69); femoral head, 0.46 (0.25–0.58); femoral neck, 0.43 (0.25–0.48); ischium, 0.45 (0.26–0.55); and pubis, 0.57 (0.45–0.65).

Conclusions: This study preliminarily established reference ranges for the ADC values of normal pelvic bony structures. The image acquisition parameters had an influence on the ADC values.

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Introduction

Quantification of image features can be used to grade the severity of a disease, to determine appropriate treatment choices, and to monitor the treatment response (1,2). The use of multiparametric magnetic resonance imaging (MRI) coupled with diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) mapping is reported to provide both functional and quantitative information about normal and tumor (primary or metastatic) tissues (3,4). Specifically, in the MRI of the pelvis, ADC maps provide a potential response biomarker that reflects the molecular characteristics of tumors and suggests the best treatment response of bone metastases from prostate cancer (PCa) (5-7).

Pelvic bony structures, including the spine (lumbar vertebra, sacrococcyx), pelvis, and femur, are reportedly the most frequent sites of bone metastases from PCa (8,9). Calculation of the ADC values of the pelvic bones is relevant for the evaluation of PCa metastases (6). Radiologists will usually extract quantitative features by drawing regions of interest (ROIs) on metastatic and normal bony tissues (without metastasis), but this process is both time-consuming and labor intensive (10). Additionally, the measurement accuracy may be hampered by differences in the experience level of clinicians. It is therefore essential to develop an automated and objective ADC analysis method that can reduce the errors of manual analysis.

The automated segmentation of pelvic bony structures is a fundamental step in both automated pelvic image analysis and quantitative information extraction. Deep learning-based convolutional neural networks (CNNs) have been widely used for organ segmentation on magnetic resonance (MR) images (11,12), and they are capable of automatically learning relevant image features to achieve image segmentation (13,14). However, few studies have been conducted on the pelvic bony structure segmentation of MR images.

An abnormality is a significant deviation from the commonly accepted patterns of a normal background tissues (15), and ADC map values are significantly different between metastatic and normal tissues (16). Despite these differences, the differentiation of normal and abnormal tissues can be difficult unless consistent and precise ADC values can be obtained from the normal tissues. In this study, we developed a deep learning method for the segmentation of pelvic bony structures on ADC maps to establish reference ranges for the ADC parameters of normal pelvic bony structures. Our aim for this study is to provide a method for the automatic measurement of the ADC values of pelvic bony structures that could be used for the future detection of abnormalities.

Methods

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the institutional review board (No. 20190701). Individual consent for this retrospective analysis was waived.

Data collection

The MR images of 944 consecutive patients who had undergone pelvic imaging for either clinically suspected or confirmed PCa between January 2018 and June 2020 were acquired from the picture archiving and communication system (PACS). The patients were selected according to the following inclusion criteria: (I) patients aged over 50 years, (II) DWI with low (b=0 s/mm^2) and high (b=800 or 1,000 s/mm^2) b values, and (III) no metastatic radiological characteristics [based on computed tomography (CT), multiparametric MR imaging (MRI) and, if available, bone scintigraphy or positron emission tomography CT (PET-CT)] within the pelvic scanning range. Patients with primary malignant bone tumors (n=24), a history of fractures or surgery (n=25), or benign lesions on pelvic bones (hemangioma: n=10; cyst: n=20; degeneration with an obvious abnormal signal: n=38; and undetermined: n=41) were not included in the analysis. Additionally, 9 patients were considered unevaluable because of incomplete DWI sequences, while 10 patients were excluded due to

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the suboptimal quality of their images (obvious motion artifacts). Finally, we performed ADC analyses of normal pelvic bony structures by using a data set of 693 patients who ranged from 50 to 95 years of age [including a subset of 288 patients randomly selected for model development (S1) and a subset of 405 patients used for model prediction (S2)]. A data set of 74 patients who received treatment [including 32 PCa patients who received radiotherapy (S3) and 42 PCa patients who received endocrine therapy (S4)] and who were not reported to have had previous pelvic bone metastases was collected for comparison with the ADC measurements. The flowchart of patient enrollment is shown in *Figure 1*.

MRI sequences

All data used in our study were anonymized. All images were axial DW images of patients in the supine position acquired from the different b values of MR scanners from 4 different vendors used at our institution with a phased-array coil [3.0 T Achieva (Philips Healthcare, the Netherlands), 3.0 T Discovery (GE Healthcare, Milwaukee, WI, USA), 1.5 T Avanto (Siemens Medical Solutions, Erlangen, Germany), and 3.0 T Interia (Philips Healthcare, the Netherlands)]. Monoexponential ADC maps were created using software from each scanner. Detailed parameters are shown in *Table 1*.

Data annotation for the deep learning model

Digital Imaging and Communications in Medicine (DICOM) images were transformed into Neuroimaging Informatics Technology Initiative (NIfTI) files before analysis, and the images were annotated using ITK-SNAP software (version 3.6.0; http://www.itksnap.org). A subset of 288 patients (no treatment) with DW images (b=800 s/mm^2 or b=1,000 s/mm^2) and ADC maps were randomly chosen and set aside for algorithmic training purposes (S1). Eight pelvic bony structures (the lumbar vertebra, sacrococcyx, ilium, acetabulum, femoral head, femoral neck, ischium, and pubis) were manually annotated in full and section by section on ADC maps (mask 1 and mask 2) by 2 radiologists (both with more than 3 years of experience). A senior radiologist (with more than 20 years of experience in pelvic imaging) modified the 2 sets of manual annotations (mask 3 and mask 4, respectively). The inter- and intrareader reliability of the manual annotations was assessed by a Dice score, which was defined as the volume of overlap divided by the union volume between the 2 masks.

Specifically, only a portion of the lumbar vertebrae that were within the pelvic scanning range were annotated, usually from the third lumbar vertebra (L3) to the fifth (L5). The number of intervertebral disc slices was relatively small and incomplete due to the large slice thickness of the DW images (6–8 mm); thus, we annotated the lumbar vertebrae continuously, which contained slices of the intervertebral disc. Since DW and ADC images were coregistered by each scanner (the ADC maps were calculated from the DW images), the manually segmented labels on the ADC maps could be matched to the DW images. The senior radiologist reviewed each DW image label that had been copied from the ADC maps and made corrections when necessary. An example of an annotation result is shown in *Figure 2*.

To count the number of pelvic bony structures, we considered the continuous lumbar vertebra to be a single structure, although it consists of 3–5 vertebrae, with the bony structures on the left and right sides considered 2 structures. Thus, there were 14 bony structures at most within scanning range of the pelvis (including 1 lumbar vertebra, 1 sacrococcyx, 2 ilia, 2 acetabula, 2 femoral heads, 2 femoral necks, 2 ischia, and 2 pubes).

Development of the deep learning model

A total of 288 DW images (b=800 or 1,000 s/mm^2) and their corresponding ADC maps were randomly selected as input to develop a 3D U-Net CNN algorithm (17) for the automated segmentation of pelvic bony structures, with each sequence considered a separate input channel. The 288 patients were randomly divided into a training set (n=232), a validation set (n=29), and a testing set (n=27) at a ratio of 8:1:1. The classical 3D U-Net architecture is detailed in Appendix 1. All the input images were unified and resized to 64×240×240 (z, y, x) before training. To train the 3D U-Net segmentation models, we exploited an Adam optimizer with an initial learning rate of 10^{-4}. The model was trained for 300 epochs until the validation loss failed to rise, and we used a fixed batch size of 2 to decrease the memory space. The tuning of other hyperparameters (such as weight initialization and dropout for regularization) was randomly searched and automatically executed in the validation set during U-Net development. The CNN was coded by Python3.6, Pytorch 0.4.1, Opencv, Numpy, and SimpleITK.

Quantitative ADC measurements

A subset of 405 patients who did not receive treatment (S2)
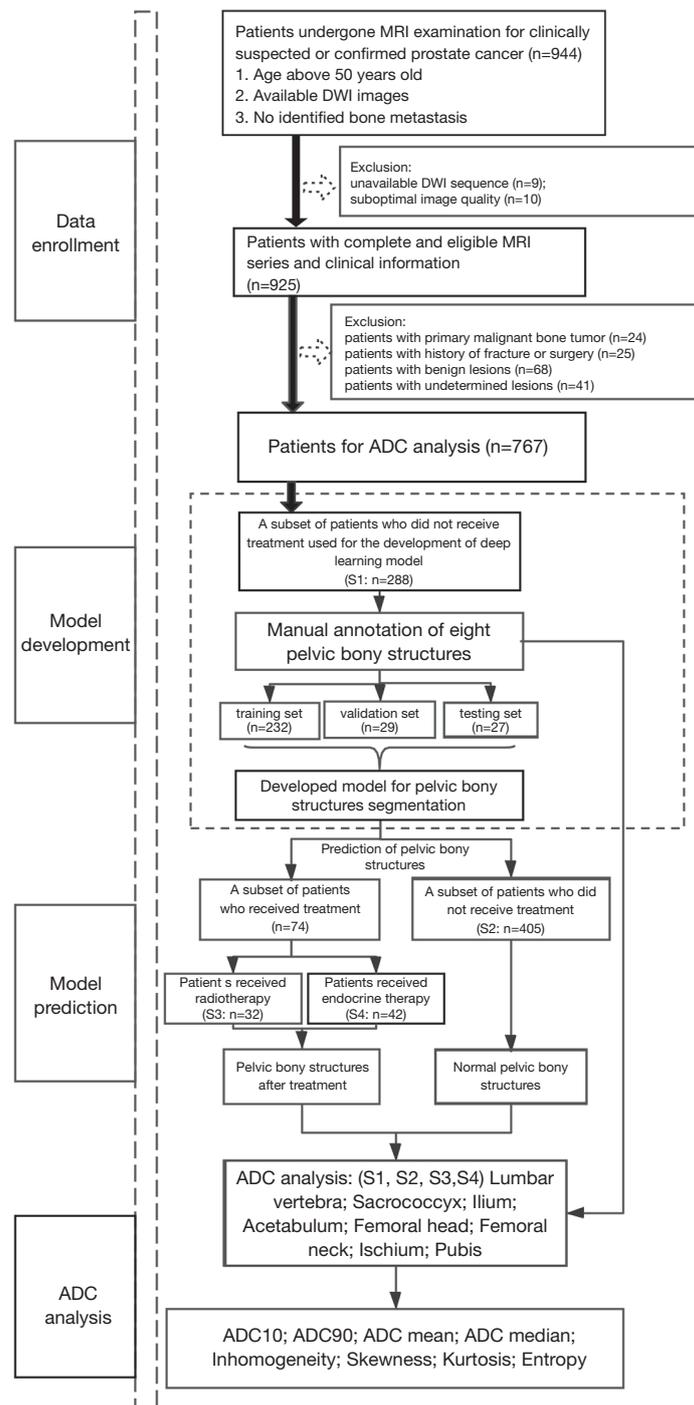
Figure 1 Workflow of the quantitative ADC analysis. S1: A subset of the 288 patients who did not receive treatment were used for model development. S2: A subset of the 405 patients who did not receive treatment were used for model prediction. S3: A subset of the 32 patients who received radiotherapy were used for model prediction. S4: A subset of the 42 patients who received endocrine therapy were used for model prediction. ADC, apparent diffusion coefficient.

Table 1 Typical parameters of the multivendor pelvis DWI sequence

Typical parameters	3.0 T Achieva (Philips Healthcare, the Netherlands)	3.0 T Discovery (Ge healthcare, Milwaukee, WI, USA)	1.5 T Avanto (Siemens Medical Solutions, Erlangen, Germany)	3.0 T Interia (Philips Healthcare, the Netherlands)
b values (s/mm^2)	0, 800	0, 800	0, 800	0, 1,000
Echo time (ms)	54	60	54	78
Repetition time (ms)	3,400	3,000	3,300	4,959
Imaging matrix	224×224	256×256	156×180	240×240
Field of view (mm)	375	360	329	360
Section thickness (mm)	6	8	7	7
Number of slices	24	25	24	28

DWI, diffusion-weighted imaging.
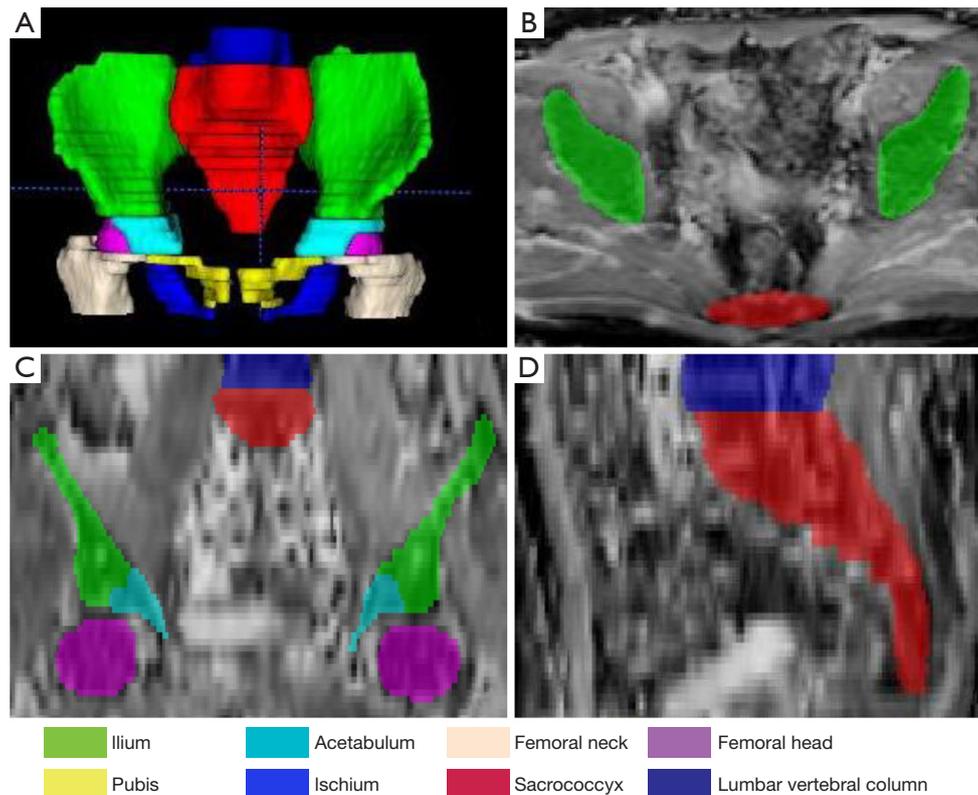
Figure 2 Manual annotations of the pelvic bony structures on ADC maps. Eight pelvic bony structures (the lumbar vertebra, sacrococcyx, ilium, acetabulum, femoral head, femoral neck, ischium, and pubis) were manually annotated by radiologists. (A) 3D spatial view of the annotated pelvic bony structures. (B) Axial view. (C) Coronal view. (D) Sagittal view. ADC, apparent diffusion coefficient.

and a subset of 74 patients who received treatment (S3 and S4) were used for pelvic bony structure segmentation by our proposed model. Before the ADC was calculated, the pelvic bony structures that were automatically segmented by the 3D U-Net CNN algorithm were manually corrected for any mistakes by the senior radiologist, who also verified that the predicted segmentation edges matched the true margins. After being manually corrected, the predicted segmentations were regarded as the reference standard to further assess the segmentation performance of the model as per the scanner and among the different groups of patients in the S2, S3, and S4 data sets.

The segmentations of the 8 pelvic bony structures on the ADC maps were regarded as volumes of interest (VOIs) for the calculation of the ADC value according to the following equation:

$$ADC = \frac{\ln\left(\frac{S0}{S1}\right)}{(b1 - b0)} \qquad [1]$$

where S1 represents the signal intensity at a particular high b value (b1=800 or 1,000 s/mm^2 in this study) and S0 represents the baseline signal without diffusion sensitization (b0=0 s/mm^2).

An ADC histogram was generated for each VOI, and the following arguments were calculated in this research: 10th percentile (ADC_{10}), 90th percentile (ADC_{90}), ADC_{mean}, ADC_{median}, inhomogeneity, skewness, kurtosis, and entropy. The concepts of these parameters are shown in Appendix 2.

To further investigate the potential factors that may influence the ADC measurements of normal pelvic bony structures, we analyzed the effect of image acquisition parameters and age on ADC measurements. To explore whether endocrine therapy or radiotherapy would affect the ADC values, we compared the ADC parameters of patients who did or did not receive treatment (patients who did not receive treatment *vs.* patients who received endocrine therapy *vs.* patients who received radiotherapy).

Statistical analysis

Statistical analyses were performed using the SPSS 22.0 software package (IBM Corp., Armonk, NY, USA). Numerical data were averaged across all the patients and are reported as the mean ± standard deviation, while a one-way analysis of variance (ANOVA) was used for both age and Dice comparisons among the different subsets and

different pelvic bony structures. For each group of ADC parameters, we used the 95% confidence interval (95% CI) to establish a reference range. The Kruskal-Wallis one-way analysis of variance (ANOVA; k-samples) with a pairwise comparison was used for multiple comparisons of the ADC parameters among the different image acquisition protocols (b value and field strength). Correlations between age, imaging parameters (b-value and field strength), treatment (with/without), and mean ADC values were analyzed by Spearman's rank-order correlation coefficient. Statistical significance was set at P<0.05.

Results

Patient characteristics

A total of 767 patients were analyzed in this research, with the patient characteristics summarized in *Table 2*. There was no significant difference in age among the 4 data sets (F=0.431, P=0.786). *Table 2* shows the detailed distribution of the bony structures from each data set.

Reliability of the manual annotations

As shown in *Table 3*, the consistency between mask 1 and mask 2 (average Dice score: 0.87±0.03) was improved after modifications were made by a senior radiologist (average Dice score between mask 3 and mask 4: 0.97±0.03). The high Dice scores of the pelvic bony structures (all above 0.95) between mask 3 and mask 4 confirmed the reliability of the manual annotations.

Segmentation accuracy of the deep learning model

Mask 4 was regarded as the reference standard for assessing the segmentation accuracy as indicated by computing the Dice scores between the CNN and manual segmentations. The Dice scores of the deep learning model for segmentation of the pelvic bony structures on the ADC maps ranged from 0.90±0.02 to 0.95±0.03 (*Figure 3*) in the testing set, with the femoral head and the femoral neck providing the highest Dice scores (0.95±0.03 and 0.94±0.03, respectively). Despite ANOVA testing revealing the scores of the ilium and the pubis to be significantly lower than those of the other regions, all the Dice scores were above 0.90.

As shown in *Table 4*, the Dice score of each pelvic bony structure was not significantly different among the different scanners in the S2 data set (P>0.05), and no significant

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Table 2 Distribution of patients and bony structures among different data sets

Characteristics	Subset of patients who did not receive treatment used for model development (n=288)			Subset of patients who did not receive treatment (n=405)	Subset of patients who received treatment (n=74)		Total (n=693)
	Training set	Validation set	Testing set		Received radiotherapy	Received endocrine therapy	
Patients							
No. of patients	232	29	27	405	32	42	693
Age (mean ± SD, years)	68.33±8.52	66.34±9.02	67.26±8.97	67.67±9.23	72.53±8.54	71.47±8.64	67.82±8.97
Pelvic bony structures							
No. of bony structures	3,166	377	341	5,569	439	580	10,472
Lumbar vertebra	212	24	22	374	23	34	689
Sacrococcyx	232	29	27	405	32	42	767
Ilium	464	58	54	810	64	84	1,534
Acetabulum	462	58	52	806	64	84	1,526
Femoral head	460	56	54	808	64	84	1,526
Femoral neck	454	54	48	796	64	84	1,500
Ischium	444	50	44	780	64	84	1,466
Pubis	438	48	40	790	64	84	1,464
Vendors							
No. of patients	232	29	27	405	32	42	693
3.0 T Achieva	12	3	3	111	10	7	146
3.0 T Discovery	155	18	15	100	6	14	308
1.5 T Avanto	43	5	6	90	9	14	167
3.0 T Interia	22	3	3	104	7	7	146

SD, standard deviation.

Table 3 The dice scores between different manual annotations

Pelvic bony structures	Mask 1 *vs.* Mask 2	Mask 1 *vs.* Mask 3	Mask 2 *vs.* Mask 4	Mask 3 *vs.* Mask 4
Lumbar vertebra	0.88±0.08	0.91±0.05	0.92±0.04	0.95±0.03
Sacrococcyx	0.88±0.06	0.90±0.03	0.89±0.05	0.98±0.01
Ilium	0.90±0.06	0.91±0.04	0.90±0.03	0.95±0.02
Acetabulum	0.88±0.06	0.91±0.03	0.91±0.05	0.96±0.01
Femoral head	0.88±0.09	0.91±0.05	0.92±0.05	0.98±0.03
Femoral neck	0.89±0.08	0.93±0.04	0.91±0.03	0.97±0.02
Ischium	0.89±0.07	0.92±0.04	0.90±0.01	0.99±0.04
Pubis	0.87±0.07	0.90±0.04	0.92±0.03	0.96±0.03
Average	0.87±0.03	0.91±0.01	0.91±0.03	0.97±0.03

Mask 1 and mask 2 were from 1 of the 2 junior radiologists, respectively; mask 3 and mask 4 were the modifications made by a senior radiologist based on mask 1 and mask 2, respectively.
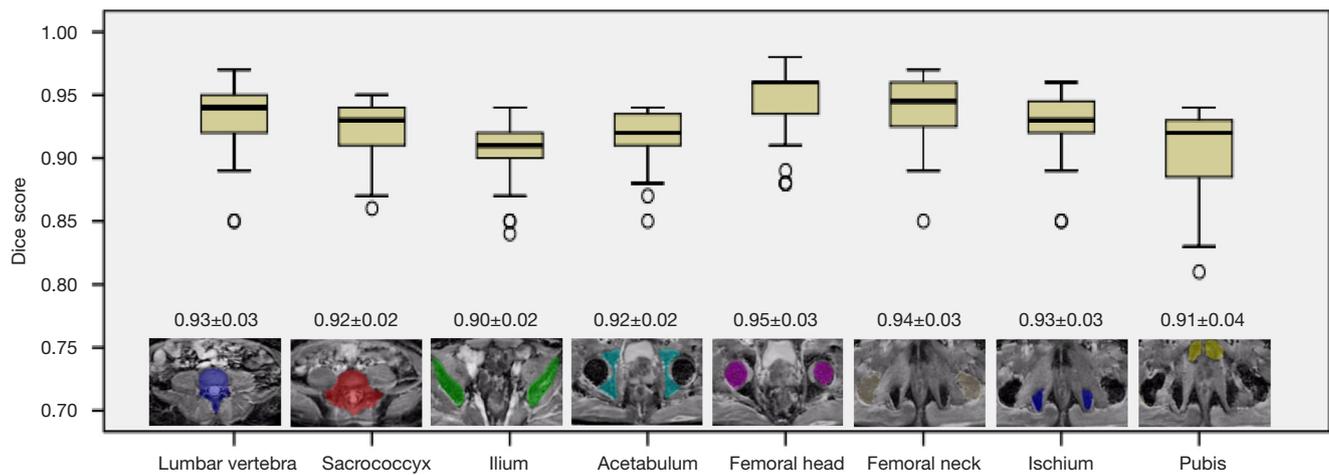
Figure 3 Dice scores for the segmentation of the pelvic bony structures. Box plots show the Dice scores for the 8 pelvic bony structures: 0.93±0.03 for the lumbar vertebra, 0.92±0.02 for the sacrococcyx, 0.90±0.02 for the ilium, 0.95±0.03 for the femoral head, 0.94±0.03 for the femoral neck, 0.93±0.03 for the ischium, and 0.91±0.04 for the pubis; o = outliers. The horizontal coordinates represent the 8 pelvic bony structures and the vertical coordinates represent the Dice scores (without units).

Table 4 Dice scores of different scanners and different groups of patients

Pelvic bony structures	S2					S3	S4	P value
	3.0 T Achieva	3.0 T Discovery	1.5 T Avanto	3.0 T Interia	P value			
Lumbar vertebra	0.92±0.03	0.93±0.04	0.92±0.04	0.92±0.03	0.918	0.91±0.04	0.91±0.03	0.349
Sacrococcyx	0.92±0.05	0.93±0.03	0.94±0.04	0.91±0.04	0.482	0.90±0.06	0.91±0.04	0.266
Ilium	0.93±0.05	0.93±0.04	0.90±0.05	0.93±0.05	0.568	0.91±0.05	0.90±0.03	0.078
Acetabulum	0.92±0.02	0.93±0.05	0.92±0.04	0.92±0.02	0.505	0.91±0.04	0.91±0.04	0.629
Femoral head	0.92±0.02	0.93±0.04	0.93±0.04	0.91±0.05	0.508	0.92±0.06	0.92±0.04	0.404
Femoral neck	0.92±0.04	0.93±0.03	0.92±0.04	0.90±0.05	0.338	0.91±0.06	0.92±0.04	0.714
Ischium	0.91±0.03	0.90±0.06	0.92±0.04	0.92±0.05	0.813	0.92±0.04	0.93±0.04	0.358
Pubis	0.90±0.04	0.92±0.03	0.92±0.04	0.90±0.03	0.596	0.92±0.05	0.91±0.05	0.770

S2: a subset of patients who did not receive treatment used for model prediction. S3: a subset of patients who received radiotherapy. S4: a subset of patients who received endocrine therapy.

differences in Dice scores were found among the S2, S3, and S4 data sets. The exemplary segmentations are shown in *Figure 4*. The high Dice scores (all above 0.95) between the automated segmentation and manually corrected segmentation indicate that the manual corrections were not extensive and required only occasional and minor corrections. The main corrections were edits on the iliac region to modify the predicted segmentation edges (*Figure 4A*).

Correlations between various parameters and mean ADC values

As shown in *Table 5*, the b values (800 and 1,000) and field strength (3.0 and 1.5 T) of the pelvic bony structures were all significantly correlated with the ADC values (all P<0.001), while age and treatment (with or without) were not significant variables (all P>0.05).
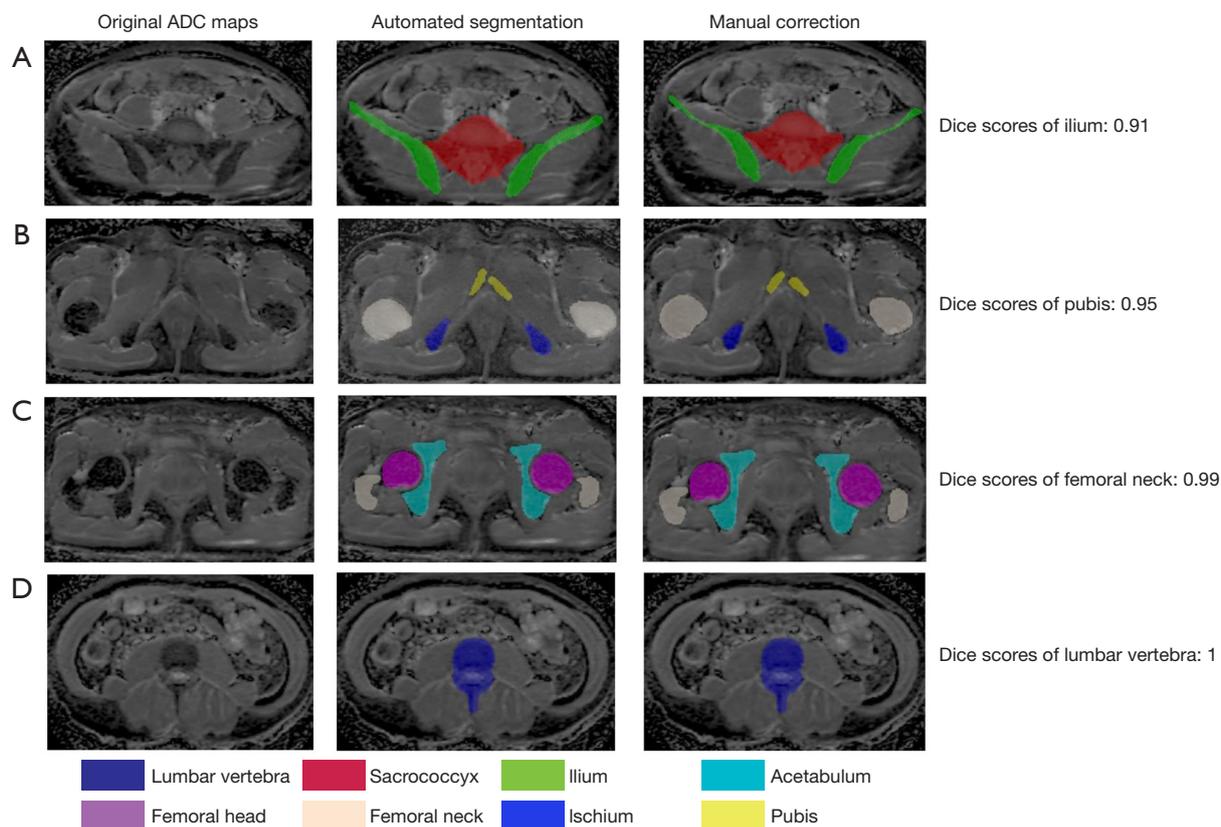
Figure 4 Examples of the comparison between the CNN predictions and the manual corrections. The comparison of the automated segmentation, the manual corrections, and the Dice scores for the different pelvic bony structures. (A) Dice scores for the ilium: 0.91; (B) Dice scores for the pubis: 0.95; (C) Dice scores for the femoral neck: 0.99; (D) Dice scores for the lumbar vertebra: 1. CNN, convolutional neural network; ADC, apparent diffusion coefficient.

Table 5 Correlations between various parameters and mean ADC values for the pelvic bony structures (R, P)

Pelvic bony structures	Age	b value	Field strength	Treatments
Lumbar vertebra	−0.055 (0.075)	0.729 (0.001)	3.323 (0.001)	0.049 (0.098)
Sacrococcyx	−0.032 (0.185)	0.657 (0.001)	0.401 (0.001)	0.014 (0.348)
Ilium	0.057 (0.057)	0.122 (0.001)	0.352 (0.001)	−0.038 (0.148)
Acetabulum	−0.019 (0.297)	0.252 (0.001)	0.550 (0.001)	−0.072 (0.054)
Femoral head	−0.029 (0.215)	0.369 (0.001)	0.635 (0.001)	−0.045 (0.109)
Femoral neck	−0.017 (0.326)	0.452 (0.001)	0.431 (0.001)	−0.052 (0.078)
Ischium	0.001 (0.499)	0.066 (0.038)	0.670 (0.001)	−0.100 (0.003)
Pubis	0.019 (0.302)	0.190 (0.001)	0.194 (0.001)	0.032 (0.191)

Unless otherwise indicated, data are correlation coefficients (R) and P values. ADC, apparent diffusion coefficient.

The effect of image acquisition parameters on ADC measurements

The ADC histogram analyses of 693 patients with normal pelvic bony structures are presented in *Table 6* for each anatomic region, which shows that the image acquisition parameters had a significant impact on the ADC measurements of pelvic bony structures. The scanner with the lowest b value and field strength also yielded the lowest mean ADC measurements on pelvic bony structures except for in the femoral neck and the ischium (lumbar vertebra: 0.93±0.12; sacrococcyx: 0.63±0.09; ilium: 0.47±0.08; acetabulum: 0.41±0.09; femoral head: 0.26±0.05; femoral neck: 0.26±0.06; ischium 0.27±0.07; and pubis: 0.50±0.08). The scanner with the highest b value and field strength (3.0 T Interia: b=1,000 s/mm^2) was shown to yield the highest mean ADC measurements on pelvic bony structures except for in the femoral neck and the ischium (lumbar vertebra: 1.52±0.16; sacrococcyx:1.13±0.14; ilium: 0.60±0.12; acetabulum: 0.66±0.12; femoral head: 0.56±0.11; and pubis: 0.63±0.12).

However, scanners with the same field strength and b value (3.0 T Achieva: b=800 s/mm^2; 3.0 T Discovery: b=800 s/mm^2) showed significant differences on ADC measurements except for the lumbar vertebra (sacrococcyx: 0.74±0.24 *vs.* 0.80±0.07; ilium: 0.49±0.17 *vs.* 0.63±0.07; acetabulum: 0.51±0.19 *vs.* 0.67±0.08; femoral head: 0.40±0.15 *vs.* 0.53±0.10; femoral neck: 0.44±0.16 *vs.* 0.50±0.08; ischium 0.44±0.16 *vs.* 0.54±0.08; and pubis: 0.49±0.18 *vs.* 0.61±0.10, all P values <0.001).

In this study, we established the reference ranges for ADC values using a general CI that contained all 4 CIs, with the lower limit of the general CI being the lowest value among the 4 CIs, and vice versa. As shown in *Table 6*, the reference ranges (95% CI) for normal pelvic bony structures were as follows: 0.90–1.54 for the lumbar vertebra, 0.61–1.15 for the sacrococcyx, 0.45–0.64 for the ilium, 0.40–0.6 for the acetabulum, 0.25-0.58 for the femoral head, 0.25–0.51 for the femoral neck, 0.26–0.55 for the ischium, and 0.45–0.65 for the pubis. Detailed comparisons of the ADC histogram parameters for the different image acquisition parameters are shown in Table S1.

Discussion

This research presents a CNN-based method for the automated segmentation of pelvic bony structures on ADC maps. Focusing on pelvic parts most commonly affected by metastases from PCa, we established a reference range for the ADC values of normal pelvic bony structures using the 95% CI for a group of patients over 50 years of age who had clinically suspected or confirmed PCa. Using the Dice score as a quantitative evaluation criterion, we found the CNN-based method in segmenting 8 pelvic bony structures performed satisfactorily, with Dice scores ranging from 0.90±0.02 to 0.95±0.03 in the testing set. Significant differences in the mean ADC values among different image acquisition parameters were observed in this study. In addition, age and treatment (with or without) were not correlated with the mean ADC values of the pelvic bony structures.

Automated segmentation of pelvic bony structures lays a foundation for subsequent quantitative ADC calculation. The automated segmentation approach for ADC maps presented herein represents a promising step toward an MRI-based quantitative analysis of bone metastases from PCa. Deep learning–based quantitative analyses on medical images reportedly have practical uses in many areas, for example, the fully automatic quantification of left ventricle function from cine MR images (18) and the automated liver biometry on CT and MR images (19). To achieve objectivity and accuracy for a quantitative analysis system, a reliable segmentation algorithm is mandatory, and it usually requires a data set with high variability for model development (18,20). In this study, a total of 767 PCa patients were recruited for ADC analysis. Completing a manual annotation of pelvic bony structure for every patient is laborious and time-consuming. Moreover, there is no clinically validated model that can be used for the automated segmentation of the 8 pelvic bony structures. Therefore, we manually annotated a subset of pelvic data (n=288) for this study and applied them for the segmentation model development, with the developed model then used to predict the rest of the pelvic data (n=479). Our results showed that the model that was trained with 288 patients achieved excellent segmentation performance in the S2, S3, and S4 data sets. The high Dice scores of the automated and manually corrected segmentations indicated that the segmentation performance of the model could achieve the same level of results as those of manual annotation.

To avoid any sampling bias caused by the selection of a localized region in the pelvic bony structures, the VOIs were determined from the ADC maps of each whole pelvic bony structure, as this may be a more reliable approach and could improve the reproducibility of the ADC value and its derivative indicators.

Table 6 Comparisons of ADC measurements for different image acquisition parameters (10^{-3} mm^2/s)

Pelvic bony structures	MRI vendors (s/mm^2)	No. of patients	ADC$_{10}$ (95% CI)	ADC$_{mean}$ (95% CI)	ADC$_{median}$ (95% CI)	ADC$_{90}$ (95% CI)
Lumbar vertebra (n=632)	3.0 T Achieva (b=800)	81	0.32±0.16 (0.37–0.44)	1.01±0.33$^&$ (0.94–1.09)	0.86±0.29$^$$ (0.80–0.92)	3.36±1.13$^&$ (3.11–3.61)
	3.0 T Discovery (b=800)	305	0.30±0.03 (0.29–0.30)	1.06±0.09$^&$ (1.05–1.07)	0.96±0.11$^&$ (0.94–0.97)	2.99±0.47$^$$ (2.94–3.04)
	1.5 T Avanto (b=800)	126	0.30±0.08 (0.29–0.32)	0.93±0.12 (0.90–0.95)	0.81±0.14$^$$ (0.78–0.83)	2.07±0.39$^$$ (2.00–2.14)
	3.0 T Intera (b=1,000)	120	0.50±0.18* (0.47–0.53)	1.52±0.16* (1.49–1.54)	1.29±0.20* (1.25–1.32)	4.52±0.75* (4.38–4.65)
	Reference range	632	–	(0.90–1.54)	–	–
Sacrococcyx (n=693)	3.0 T Achieva (b=800)	111	0.38±0.14$^&$ (0.35–0.41)	0.74±0.24$^&$ (0.70–0.79)	0.58±0.19$^$$ (0.54–0.61)	2.87±0.88$^&$ (2.70–3.04)
	3.0 T Discovery (b=800)	308	0.24±0.02$^$$ (0.24–0.25)	0.80±0.07$^&$ (0.79–0.81)	0.68±0.08$^&$ (0.67–0.69)	2.45±0.31$^$$ (2.42–2.48)
	1.5 T Avanto (b=800)	142	0.19±0.04 (0.18–0.19)	0.63±0.09 (0.61–0.64)	0.51±0.08 (0.50–0.52)	1.87±0.34 (1.81–1.92)
	3.0 T Intera (b=1,000)	132	0.49±0.18* (0.46–0.52)	1.13±0.14* (1.10–1.15)	0.84±0.13* (0.82–0.86)	3.83±0.71* (3.72–3.96)
	Reference range	693	–	(0.61–1.15)	–	–
Ilium (n=1,386)	3.0 T Achieva (b=800)	111	0.28±0.10$^&$ (0.26–0.29)	0.49±0.17 (0.45–0.52)	0.38±0.15 (0.35–0.41)	2.09±0.65$^&$ (1.97–2.21)
	3.0 T Discovery (b=800)	308	0.23±0.02$^$$ (0.22–0.24)	0.63±0.07* (0.62–0.64)	0.51±0.07* (0.51–0.52)	2.22±0.22$^&$ (0.20–0.25)
	1.5 T Avanto (b=800)	142	0.15±0.03 (0.15–0.16)	0.47±0.08 (0.46–0.48)	0.40±0.08 (0.39–0.42)	1.36±0.15$^$$ (1.34–1.39)
	3.0 T Intera (b=1,000)	132	0.32±0.11* (0.30–0.34)	0.60±0.12* (0.58–0.62)	0.47±0.11* (0.45–0.49)	2.62±0.44* (2.54–2.69)
	Reference range	693	–	(0.45–0.64)	–	–
Acetabulum (n=1,378)	3.0 T Achieva (b=800)	111	0.25±0.08* (0.23–0.26)	0.51±0.19$^&$ (0.47–0.54)	0.40±0.17$^$$ (0.37–0.43)	1.94±0.62* (1.82–2.05)
	3.0 T Discovery (b=800)	304	0.19±0.03$^&$ (0.18–0.19)	0.67±0.08* (0.66–0.68)	0.56±0.08* (0.55–0.57)	1.78±0.18$^&$ (1.76–1.80)
	1.5 T Avanto (b=800)	142	0.12±0.03$^$$ (0.12–0.13)	0.41±0.09$^$$ (0.40–0.43)	0.34±0.09 (0.33–0.36)	1.20±0.18$^$$ (1.17–1.23)
	3.0 T Intera (b=1,000)	132	0.25±0.08* (0.23–0.26)	0.66±0.12* (0.64–0.69)	0.52±0.11$^&$ (0.50–0.54)	2.31±0.41* (2.24–2.39)
	Reference range	689	–	(0.40–0.69)	–	–
Femoral head (n=1,378)	3.0 T Achieva (b=800)	111	0.23±0.08* (0.21–0.24)	0.40±0.15$^$$ (0.37–0.43)	0.25±0.13$^$$ (0.22–0.27)	1.72±0.54$^&$ (1.61–1.82)
	3.0 T Discovery (b=800)	304	0.16±0.03$^&$ (0.15–0.16)	0.53±0.10$^&$ (0.51–0.53)	0.40±0.12$^&$ (0.39–0.41)	1.73±0.21$^$$ (1.71–1.76)
	1.5 T Avanto (b=800)	142	0.08±0.02$^$$ (0.08–0.09)	0.26±0.05 (0.25–0.27)	0.15±0.07 (0.14–0.16)	1.00±0.15$^$$ (0.98–1.03)
	3.0 T Intera (b=1,000)	132	0.24±0.07* (0.23–0.25)	0.56±0.11* (0.55–0.58)	0.45±0.10* (0.43–0.47)	2.09±0.43* (2.01–2.16)
	Reference range	689	–	(0.25–0.58)	–	–

Table 6 (*continued*)

Table 6 (*continued*)

Pelvic bony structures	MRI vendors (s/mm²)	No. of patients	ADC$_{10}$ (95% CI)	ADC$_{mean}$ (95% CI)	ADC$_{median}$ (95% CI)	ADC$_{90}$ (95% CI)
Femoral neck (n=1,352)	3.0 T Achieva (b=800)	110	0.24±0.08* (0.22–0.25)	0.44±0.16& (0.41–0.47)	0.33±0.13& (0.30–0.36)	1.87±0.64* (1.75–1.99)
	3.0 T Discovery (b=800)	293	0.18±0.02& (0.18–0.19)	0.50±0.08* (0.49–0.51)	0.36±0.09* (0.35–0.37)	1.96±0.24* (1.93–1.99)
	1.5 T Avanto (b=800)	141	0.11±0.01$ (0.10–0.11)	0.26±0.06$ (0.25–0.27)	0.14±0.09$ (0.12–0.16)	1.13±0.13 (1.11–1.15)
	3.0 T Intera (b=1,000)	132	0.23±0.08* (0.22–0.24)	0.47±0.07& (0.45–0.48)	0.36±0.07* (0.34–0.37)	2.02±0.39* (1.96–2.09)
	Reference range	676	–	(0.25–0.51)	–	–
Ischium (n=1,318)	3.0 T Achieva (b=800)	101	0.18±0.06* (0.17–0.19)	0.44±0.16& (0.41–0.47)	0.35±0.14& (0.32–0.38)	1.51±0.49* (1.41–1.60)
	3.0 T Discovery (b=800)	286	0.16±0.02* (0.15–0.16)	0.54±0.08* (0.53–0.55)	0.44±0.07* (0.43–0.45)	1.56±0.18* (1.54–1.58)
	1.5 T Avanto (b=800)	140	0.08±0.02 (0.08–0.09)	0.27±0.07$ (0.26–0.28)	0.20±0.10$ (0.19–0.22)	0.90±0.12 (0.88–0.92)
	3.0 T Intera (b=1,000)	132	0.18±0.06* (0.17–0.19)	0.46±0.09& (0.45–0.48)	0.36±0.09& (0.34–0.37)	1.64±0.33* (1.59–1.70)
	Reference range	659	–	(0.26–0.55)	–	–
Pubis (n=1,316)	3.0 T Achieva (b=800)	100	0.19±0.07 (0.17–0.20)	0.49±0.18& (0.45–0.52)	0.43±0.18& (0.40–0.47)	1.40±0.48& (1.30–1.49)
	3.0 T Discovery (b=800)	286	0.21±0.07* (0.20–0.22)	0.61±0.10* (0.60–0.62)	0.56±0.10* (0.55–0.58)	1.21±0.14& (1.19–1.22)
	1.5 T Avanto (b=800)	140	0.24±0.07* (0.23–0.26)	0.50±0.08& (0.48–0.51)	0.45±0.08& (0.44–0.47)	0.88±0.12$ (0.86–0.90)
	3.0 T Intera (b=1,000)	132	0.23±0.08* (0.21–0.24)	0.63±0.12* (0.61–0.65)	0.57±0.12* (0.55–0.59)	1.56±0.29* (1.51–1.61)
	Reference range	658	–	(0.45–0.65)	–	–

The symbols "*", "&", and "$" represent the values from high to low with significant differences (*, in the significantly highest value among the 4 groups; &, in the second highest value; $, in the third highest value, value without symbol indicates the lowest value). Data with the same symbol indicates that the difference was not significant. ADC, apparent diffusion coefficient.

The value of quantitative ADC measurements has been well demonstrated, especially in differentiating the diagnoses and prognoses of different cancers. Assessments with ADC histograms might provide more reliable results that reflect the biological characteristics of heterogeneous lesions (21,22). Despite numerous studies on quantitative ADC analyses, there is a lack of sufficiently robust data on the reference range derived from normal pelvic bony structures. Our study showed that the reference ranges of ADC values for normal pelvic structures could be defined as follows: $(0.90–1.54)\times10^{-3}$ mm^2/s for the lumbar vertebra, $(0.61–1.15)\times10^{-3}$ mm^2/s for the sacrococcyx, $(0.45–0.64)\times10^{-3}$ mm^2/s for the ilium, $(0.40–0.69)\times10^{-3}$ mm^2/s for the acetabulum, $(0.25–0.58)\times10^{-3}$ mm^2/s for the femoral head, $(0.25–0.51)\times10^{-3}$ mm^2/s for the femoral neck, $(0.26–0.55)\times10^{-3}$ mm^2/s for the ischium, and $(0.45–0.65)\times10^{-3}$ mm^2/s for the pubis.

A previously conducted study reported similar reference ranges to these (16), and defined normal ADC values of $(0.43±0.17)\times10^{-3}$ mm^2/s for the iliac crest, $0.33±0.20\times10^{-3}$ mm^2/s for the lumbar vertebrae, and $(0.21±0.16)\times10^{-3}$ mm^2/s for the femur in healthy subjects (n=32). These values were outside the lower limit of the reference ranges reported in our study, which might have been due to the lower b value (400 s/mm^2) of DW images used to create the ADC maps. A large difference was observed for the lumbar vertebrae [0.33 *vs.* (0.90–1.54)], as the structure of the lumbar vertebrae in our study contained slices of the vertebral body and disc, resulting in larger ADC values. The upper limit of the reference range is more meaningful than is the lower limit, because metastatic lesions can increase the ADC value of bony structures (23,24). Thus, various research results should be integrated to obtain a universal upper limit of normal bony structures as a threshold for a differential diagnosis across all involved vendors.

We found that different image acquisition parameters including both the diffusion coefficient b value and field strength could have influenced the ADC measurements, as it has been proven that ADC values may differ among the imaging phantoms of different MRI systems (25). Given the statistical differences found among the 4 different scanners, 4 normal distributions of ADC values with 4 CIs were established in this study. However, according to the CIs shown in *Table 6*, the reference ranges among the different scanners overlap, owing to the interaction of the b value and field strength. Thus, specifying the reference range of each scanner as per their b value and field strength is considered to be overly complicated. Additionally, the

statistical differences among the scanners showed no clinical significance and were far fewer in number than the ADC differences between the normal and metastatic pelvic bony structures. Similarly, Messiou *et al.* (26) established a normal pelvic bone ADC value of $(0.47±0.14)\times10^{-3}$ mm^2/s and a metastatic ADC value of $(0.98±0.36)\times10^{-3}$ mm^2/s. The difference (approximately 0.51×10^{-3} mm^2/s) between the normal and metastatic bones was larger than the difference observed between the different scanners (as shown in *Table 6*). Additionally, Nonomura *et al.* (27) found that the ADC difference in the ilium between the normal and metastatic marrow on a 1.5T MR system was 0.48×10^{-3} mm^2/s (0.8 "versus" 1.3), which was much larger than the ADC difference in the ilium found between the 1.5 and 3.0 T scanners (0.16×10^{-3} mm^2/s). Therefore, this study established general reference ranges for the ADC values that contained all 4 CIs, which is more practicable in clinical settings. While the reference ranges for the ADC values established in this study were applicable for patients in whom the same scanning parameters were used (field strength and b values), the type of MR scanner and imaging protocol should be considered when applying the reference range to clinical practice. Since a specific and widely accepted protocol for quality controls in DWI is still lacking (28), the development of a set of quality control procedures is critical to successful validation if the ADC is to become a useful biomarker in the future (29).

In this study, patient age (>50 years) did not seem to be a statistically significant influence on the ADC measurements, which was inconsistent with the conclusion drawn by Lavdas *et al.*, who noted that the ADCs of bone marrow show significant change with age (10). This discrepancy might be due to the difference in the age range of the patients enrolled in this study. Considering that PCa is more likely to develop in older patients (30,31), we chose to recruit patients for our research that were older than 50 (mean age 67.82±8.97 years, range 50–85 years), while those in the study by Lavdas *et al.* were younger (mean age 38 years, range 23–68 years). The age-related bone marrow conversion pattern varies by age group and body part; thus, if the reference range can be specified to a specific patient population, it could aid in diagnosis and differential pathology (32).

We recognize several limitations of this study. First, the manual annotations of the 8 pelvic bony structures were based on the anatomical knowledge of the clinicians attached to this study, which introduced a certain degree of subjectivity. Second, for ADC quantification of the lumbar

vertebrae and sacrococcyx, we did not exclude the areas of the intervertebral disc and the spinal canal, resulting in higher ADC values of the lumbar vertebra and sacrococcyx. In future studies, spinal canal and intervertebral disc segmentation should be used to further improve the accuracy of ADC analyses. Third, the number of patients who received radiotherapy and endocrine therapy and were also subjected to ADC analysis was small, so a larger sample is needed to establish reference ranges for these patient types. Fourth, selection bias might have been present because all patients in this study were over 50 years of age, and ADC parameters from younger patients were not analyzed.

In conclusion, we established reference ranges of ADC values for normal pelvic bony structures by using a deep learning-based method. The algorithms and measurements presented in this article could provide a basis for developing quantitative radiologic reports in the future.

Acknowledgments

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/qims-21-123). YZ and XW from the commercial company, Beijing Smart Tree Medical Technology Co. Ltd, were collaborating scientists providing technical support under the collaboration regulations and had no financial or other conflicts of interests with respect to this study. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by institutional review board (No. 20190701). Individual consent for this retrospective analysis was waived.

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Appendix 1

Deep learning architecture

The classical network consisted of encoding blocks, decoding blocks, an initial convolution layer, and a final convolution layer. Each dense block was composed of a convolution layer, batch normalization, rectified linear unit activation layers, and pooling layer or upsampling layer. The layers of each block were densely connected. The input to a dense block was also concatenated with the output to the block itself. The input of each decoding block contained the output of the upsampled activation values and a concatenation with the corresponding feature maps of the encoding path, which are also known as skip connections.

Appendix 2

Conceptions of ADC histogram parameters

Histogram analysis is a method used to provide images with more information that is often overlooked by the human eye. The grayscale distribution in the ROI of the obtained image data was evaluated by mathematical methods to quantify the heterogeneity of the pathological changes (33,34).

- (I) The nth percentile: the point at which n% of the voxel values from the histogram are found on the left of the histogram.
- (II) Inhomogeneity: the standard deviation divided by the mean signal intensity across all pixels.
- (III) Skewness represents the asymmetry of deviation from the normal distribution of a histogram. If the majority of the data are concentrated on the left of the histogram, the skewness value is positive, while the value is negative if the majority of data are concentrated on the right of the histogram.
- (IV) Kurtosis represents the peakedness of a histogram and is categorized as follows: values that are equal to 3 indicate the histogram is Gaussian, values greater than 3 indicate a sharper peak, and values less than 3 indicate a flatter top.
- (V) Entropy reflects the irregularity of ADC value distribution within an ADC histogram.

References

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Table S1 Comparisons of ADC histogram parameters for different image acquisition parameters

Pelvic bony structures	MRI vendors (s/mm²)	No. of patients	ADC_{10} (10^{-3} mm²/s)	ADC_{mean} (10^{-3} mm²/s)	ADC_{median} (10^{-3} mm²/s)	ADC_{90} (10^{-3} mm²/s)	Inhomogeneity	Skewness	Kurtosis	Entropy
Lumbar vertebra (n=632)	3.0 T Achieva (b=800)	81	0.32±0.16	1.01±0.33$^{\&}$	0.86±0.29$^{\$}$	3.36±1.13$^{\&}$	0.87±0.10*	1.30±0.34	2.11±1.42$^{\$}$	8.94±0.59$^{\$}$
	3.0 T Discovery (b=800)	305	0.30±0.03	1.06±0.09$^{\&}$	0.96±0.11$^{\&}$	2.99±0.47$^{\$}$	0.71±0.08$^{\&}$	1.44±0.40	3.51±1.92*	10.64±0.25*
	1.5 T Avanto (b=800)	126	0.30±0.08	0.93±0.12	0.81±0.14$^{\$}$	2.07±0.39$^{\$}$	0.67±0.11$^{\&}$	1.42±0.42	2.92±1.69$^{\&}$	10.06±0.44$^{\&}$
	3.0 T Intera (b=1,000)	120	0.50±0.18*	1.52±0.16*	1.29±0.20*	4.52±0.75*	0.85±0.09*	1.40±0.32	2.41±1.24$^{\$}$	10.07±0.54$^{\&}$
Sacrococcyx (n=693)	3.0 T Achieva (b=800)	111	0.38±0.14$^{\&}$	0.74±0.24$^{\$}$	0.58±0.19$^{\$}$	2.87±0.88$^{\&}$	0.95±0.08*	1.27±0.25$^{\$}$	2.02±1.19$^{\$}$	8.49±0.57$^{\$}$
	3.0 T Discovery (b=800)	308	0.24±0.02$^{\$}$	0.80±0.07$^{\&}$	0.68±0.08$^{\&}$	2.45±0.31$^{\$}$	0.74±0.06	1.18±0.31	2.25±1.56$^{\$}$	10.55±0.21*
	1.5 T Avanto (b=800)	142	0.19±0.04	0.63±0.09	0.51±0.08	1.87±0.34	0.78±0.11$^{\$}$	1.79±0.45*	5.37±2.47*	10.05±0.31$^{\&}$
	3.0 T Intera (b=1,000)	132	0.49±0.18*	1.13±0.14*	0.84±0.13*	3.83±0.71*	0.93±0.07$^{\&}$	1.40±0.32*	2.64±1.60$^{\&}$	9.71±0.67$^{\&}$
Ilium (n=1,386)	3.0 T Achieva (b=800)	111	0.28±0.10$^{\&}$	0.49±0.17	0.38±0.15	2.09±0.65$^{\&}$	1.01±0.09*	1.22±0.20	1.80±1.03$^{\$}$	7.15±0.77
	3.0 T Discovery (b=800)	308	0.23±0.02$^{\$}$	0.63±0.07*	0.51±0.07*	2.22±0.22$^{\&}$	0.83±0.08$^{\&}$	1.34±0.24*	2.68±1.26$^{\&}$	10.01±0.34*
	1.5 T Avanto (b=800)	142	0.15±0.03	0.47±0.08	0.40±0.08	1.36±0.15$^{\$}$	0.70±0.15$^{\$}$	1.11±0.24$^{¥}$	1.47±0.86$^{\$}$	9.59±0.46$^{\&}$
	3.0 T Intera (b=1,000)	132	0.32±0.11*	0.60±0.12*	0.47±0.1*	2.62±0.44*	1.00±0.11*	1.71±0.35*	4.48±2.07*	8.23±0.91$^{\$}$
Acetabulum (n=1,378)	3.0 T Achieva (b=800)	111	0.25±0.08	0.51±0.19$^{\&}$	0.40±0.17*	1.94±0.62*	1.01±0.09*	1.17±0.19$^{\$}$	1.51±0.77	6.96±0.68
	3.0 T Discovery (b=800)	304	0.19±0.03$^{\&}$	0.67±0.08*	0.56±0.08*	1.78±0.18$^{\&}$	0.79±0.08$^{\$}$	1.19±0.30$^{\$}$	2.19±1.56$^{\$}$	9.76±0.31*
	1.5 T Avanto (b=800)	142	0.12±0.03$^{\$}$	0.41±0.09$^{\$}$	0.34±0.09	1.20±0.18$^{\$}$	0.89±0.18$^{\&}$	1.37±0.35$^{\&}$	2.60±1.67$^{\&}$	8.70±0.70$^{\&}$
	3.0 T Intera (b=1,000)	132	0.25±0.08*	0.66±0.12*	0.52±0.11$^{\&}$	2.31±0.41*	0.98±0.09*	1.50±0.26*	2.85±1.14*	8.18±0.72$^{\$}$
Femoral head (n=1,378)	3.0 T Achieva (b=800)	111	0.23±0.08	0.40±0.15$^{\$}$	0.25±0.13*	1.72±0.54$^{\&}$	1.16±0.10*	1.24±0.19$^{\$}$	1.37±0.75$^{\$}$	5.87±0.49$^{\$}$
	3.0 T Discovery (b=800)	304	0.16±0.03$^{\&}$	0.53±0.10$^{\&}$	0.40±0.12$^{\&}$	1.73±0.21$^{\&}$	1.03±0.16$^{\&}$	1.55±0.48$^{\&}$	3.67±2.95*	8.70±0.60*
	1.5 T Avanto (b=800)	142	0.08±0.02$^{\$}$	0.26±0.05	0.15±0.07	1.00±0.15$^{\$}$	1.24±0.17*	1.69±0.33*	3.42±1.76$^{\&}$	7.08±0.80$^{\&}$
	3.0 T Intera (b=1,000)	132	0.24±0.07*	0.56±0.11*	0.45±0.10*	2.09±0.43*	1.01±0.09$^{\&}$	1.50±0.29$^{\&}$	3.36±1.63$^{\&}$	7.43±0.72$^{\&}$
Femoral neck (n=1,352)	3.0 T Achieva (b=800)	110	0.24±0.08*	0.44±0.16$^{\&}$	0.33±0.13*	1.87±0.64*	1.07±0.08	1.26±0.20*	1.86±0.94$^{\$}$	6.49±0.41
	3.0 T Discovery (b=800)	293	0.18±0.02$^{\&}$	0.50±0.08*	0.36±0.09*	1.96±0.24*	1.07±0.12	1.64±0.33$^{\&}$	3.94±2.14*	8.81±0.64*
	1.5 T Avanto (b=800)	141	0.11±0.01$^{\$}$	0.26±0.06$^{\$}$	0.14±0.09$^{\$}$	1.13±0.13	1.27±0.21*	1.61±0.44*	3.40±2.30$^{\&}$	6.83±0.90$^{\$}$
	3.0 T Intera (b=1,000)	132	0.23±0.08*	0.47±0.07$^{\&}$	0.36±0.07*	2.02±0.39*	1.06±0.08	1.67±0.33*	4.57±2.45*	7.40±0.73$^{\&}$
Ischium (n=1,318)	3.0 T Achieva (b=800)	101	0.18±0.06*	0.44±0.16$^{\&}$	0.35±0.14$^{\&}$	1.51±0.49*	1.01±0.10*	1.06±0.20*	1.04±0.91$^{\$}$	6.59±0.63$^{\$}$
	3.0 T Discovery (b=800)	286	0.16±0.02*	0.54±0.08*	0.44±0.07*	1.56±0.18*	0.87±0.10	1.31±0.27$^{\&}$	2.36±1.42*	9.31±0.40*
	1.5 T Avanto (b=800)	140	0.08±0.02	0.27±0.07$^{\$}$	0.20±0.10$^{\$}$	0.90±0.12	1.07±0.22*	1.30±0.32$^{\&}$	1.87±1.32$^{\&}$	7.42±0.94$^{\&}$
	3.0 T Intera (b=1,000)	132	0.18±0.06*	0.46±0.09$^{\&}$	0.36±0.09$^{\&}$	1.64±0.33*	1.03±0.10*	1.38±0.31*	2.61±1.82*	7.32±0.78$^{\&}$
Pubis (n=1,316)	3.0 T Achieva (b=800)	100	0.19±0.07	0.49±0.18$^{\&}$	0.43±0.18$^{\&}$	1.40±0.48$^{\&}$	0.84±0.13*	0.85±0.25$^{\&}$	0.80±1.14$^{\&}$	6.84±0.73
	3.0 T Discovery (b=800)	286	0.21±0.07*	0.61±0.10*	0.56±0.10*	1.21±0.14$^{\&}$	0.58±0.11$^{\$}$	0.80±0.37$^{\&}$	1.33±1.61*	9.41±0.32*
	1.5 T Avanto (b=800)	140	0.24±0.07*	0.50±0.08$^{\&}$	0.45±0.08$^{\&}$	0.88±0.12$^{\$}$	0.45±0.10	0.88±0.27$^{\&}$	0.99±0.86$^{\&}$	8.64±0.25$^{\&}$
	3.0 T Intera (b=1,000)	132	0.23±0.08*	0.63±0.12*	0.57±0.12*	1.56±0.29*	0.74±0.11$^{\&}$	0.92±0.30	1.33±1.37*	7.82±0.86$^{\$}$

All pairwise Kruskal-Wallis one-way ANOVA (k-samples) were used for multiple comparisons of the 4 scanners for the ADC parameters. The symbols "*", "&", and "$" represent the values from high to low with significant difference (*, indicates the significantly highest value among the 4 groups; &, indicates the second highest value; $, indicates the third highest value, and no symbol indicates the lowest value). Data with the same symbol indicates that the difference was not significant.