




# A Cross-Sectional Study to Evaluate Diffusion Tensor Imaging Findings of the Brain in End-Stage Renal Disease (ESRD) Patients Undergoing Maintenance Hemodialysis Using Volume of Interest Method

Tushar Dighe<sup>1</sup>, Tushar Kalekar<sup>2</sup>, Rajesh Kuber<sup>2</sup>, Debapriya Saha <sup>1,\*</sup>, Nilesh Shinde<sup>1</sup>, Pavan Wakhare<sup>1</sup>, Charan Bale<sup>1</sup> and Atul Sajgure<sup>1</sup>

<sup>1</sup>Department of Nephrology, Dr. D. Y. Patil Medical College, Hospital & Research Centre, Pimpri-Chinchwad, India

<sup>2</sup>Department of Radiology, Dr. D. Y. Patil Medical College, Hospital & Research Centre, Pimpri-Chinchwad, India

\*Corresponding author: Department of Nephrology, Dr. D. Y. Patil Medical College, Hospital & Research Centre, Pimpri-Chinchwad, India. Email: drdebapriyasaha@drpksahahosp.in

Received 2023 November 25; Revised 2024 February 19; Accepted 2024 March 17.

## Abstract

**Background:** Cerebral small vessel disease (CSVD) is a chronic disorder affecting small vessels within the brain, increasing the risk of stroke in patients with chronic kidney disease (CKD). Diffusion tensor imaging (DTI) is a newer quantitative method for diagnosing CSVD at an early stage of pathogenesis.

**Objectives:** This study compares various DTI parameters in multiple white matter tracts of the brain in CKD patients undergoing maintenance hemodialysis with normal controls in the Indian population using the volume of interest (VOI) method. Additionally, it correlates these DTI parameters with each other at different locations to gain insights into the pathogenesis of CSVD.

**Methods:** After obtaining institutional ethics approval, a cross-sectional study was conducted at a tertiary care hospital over one year (June 2022 to May 2023). The study comprised seventy-five patients in the hemodialysis group and twenty-five controls. All participants underwent MRI brain examinations on a 3 Tesla MRI scanner, and the four DTI parameters - fractional anisotropy (FA), axial diffusivity (AD), radial diffusivity (RD), and mean diffusivity (MD) - were reviewed for nine white matter tracts to evaluate statistical differences and correlations.

**Results:** Fractional anisotropy was significantly decreased at anterior locations - corpus callosum genu ( $P = 0.357 \times 10^{-7}$ ), right anterior corona radiata ( $P = 0.001$ ), and left anterior corona radiata ( $P = 0.45 \times 10^{-5}$ ). In these locations, FA negatively correlated with RD ( $R = -0.7904$ ,  $P < 0.00001$ ), and RD was also significantly increased. Axial diffusivity was significantly increased at posterior locations in the corpus callosum splenium ( $P = 0.108 \times 10^{-5}$ ) and left posterior corona radiata ( $P = 0.244 \times 10^{-5}$ ). However, none of the four DTI parameters showed significant differences between hemodialysis patients and the control group for the subset of patients with normal routine brain MRI features. The intraclass correlation coefficients (ICCs) were high for all four DTI parameters for both patients (0.78 to 0.85) and controls (0.82 to 0.89).

**Conclusions:** This study on CKD patients undergoing maintenance hemodialysis reveals significant differences in some DTI parameters in widespread white matter tracts of the brain using the VOI method, with acceptable to excellent interobserver agreement.

**Keywords:** Diffusion Tensor Imaging, Renal Dialysis, Renal Insufficiency

## 1. Background

With the continuous rise of chronic kidney disease (CKD) among the list of causes of death, it is estimated that CKD will become the fifth highest cause of years of life lost globally by 2040 (1). Compared to the healthy population, the risk of stroke is 5 - 30 times higher in CKD patients on maintenance hemodialysis, with

corresponding case fatality rates as high as 90%. Cerebral small vessel disease (CSVD) is a chronic disorder of small vessels with a diameter between 50 - 400  $\mu\text{m}$  within the brain and results in a more than threefold independent increase in the risk of stroke (2). Cerebral small vessel disease in the brain is diagnosed through a routine MRI scan using the STRIVE protocol (Standards for Reporting Vascular Changes on Neuroimaging). Diffusion tensor

imaging (DTI) is a relatively newer MRI imaging modality of the brain that focuses on evaluating restrictions in the direction of Brownian motion of water molecules as an early surrogate marker of white matter tract integrity in the brain (3).

Fractional anisotropy (FA), axial diffusivity (AD), radial diffusivity (RD), and mean diffusivity (MD) are four parameters of DTI investigation. In recent studies, white matter tracts have shown decreased FA in CKD patients (4-7) because of CSVD. Additionally, few studies have correlated these changes depicted by DTI analysis with clinical parameters of neurocognition (5, 8). Therefore, DTI is a new quantitative imaging modality that can potentially be used for the early detection of white matter disease due to CSVD in CKD patients. However, most recent studies on DTI are conducted using the tract-based spatial statistics (TBSS) method, which is an excellent research tool for group analysis of DTI patients but is complicated and cannot be tested on a single patient. We attempted to calculate DTI parameters using commercially available software using the volume of interest (VOI) method (9). We investigated the null hypothesis that the DTI parameters - FA, MD, RD, AD in white matter tracts of CKD patients on (CKD-maintenance hemodialysis [MHD]) are not significantly different from those in the control population with normal renal function (NC) in the Indian population.

## 2. Objectives

Our additional objective was to correlate these DTI parameters with each other to gain insights into the pathogenesis of CSVD in the brain in dialysis patients in the Indian population. Moreover, numerous studies have found DTI to be a better marker for CSVD than conventional MRI findings (10-12). In a subgroup of CKD-MHD patients with normal routine MRI, we attempted to find if DTI parameters in the brain are significantly different from healthy controls.

## 3. Methods

### 3.1. Case and Control Selection

After securing institutional ethics approval (IESC/S.SP/2019/02 dated 25.05.21), a cross-sectional study with a study design illustrated in [Figure 1](#) was conducted in a tertiary care hospital for a period of one year (June 2022 to May 2023) based on the well-known strengthening the reporting of observational studies in epidemiology (STROBE) guidelines. During this period, consecutive adult patients with chronic end-stage renal disease who were

enrolled for hemodialysis at our center were included in the study as cases if they provided informed consent, were on maintenance hemodialysis for more than three months, and did not have the following exclusion criteria: Contraindication for 3T MRI, a previous history of stroke, traumatic brain injury, or any neurosurgical procedure, autosomal dominant polycystic kidney disease, chronic infection, or malignant disease. Controls were recruited from hospital visitors aged between 18 and 75 years with normal renal function and normal urine analysis. The exclusion criteria for controls were the same as those for cases.

### 3.2. Sample Size

In a previous study (7), the mean and standard deviation of FA values at the genu of the corpus callosum in healthy controls and end-stage chronic kidney patients were  $0.67 \pm 0.04$  and  $0.6 \pm 0.06$ , respectively. To achieve 80% power with a 5% level of significance and a design ratio of 2.5:1 for sample to control, a minimum sample size of thirteen patients and five controls was required. We set a sample size of 75 patients and 25 controls, exceeding the minimum required sample size.

### 3.3. Methodology

The clinical history, physical examination, and biochemical studies were recorded in a predetermined format. All patients underwent an MRI Brain examination on a 3 Tesla MRI scanner (MAGNETOM Vida, Siemens Healthineers, Erlangen, Germany) immediately before the scheduled hemodialysis session.

### 3.4. Technique of MRI Examination

MRI Brain routine and DTI sequences were acquired in the same setting using the standard Siemens head coil with 32 channels. MRI brain routine sequences included T1 axial, T2 axial, fluid-attenuated inversion recovery (FLAIR) axial, susceptibility-weighted imaging (SWI), diffusion-weighted imaging (DWI), and apparent diffusion coefficient (ADC) sequences. Diffusion tensor imaging acquisition was performed using multidirectional diffusion-weighted sequences (MDDW) echo planar imaging with 20 tensor directions and two diffusion B values (0, 1 000) with 12 and 3 averages for each of the two B values, respectively.

### 3.5. Data Postprocessing and Image Analysis

The DTI data were transferred to the workstation (Syngo MR XA31, Erlangen, Germany). First, the multidirectional diffusion series was visually analyzed for artifacts. Then, any distortions detected by the software

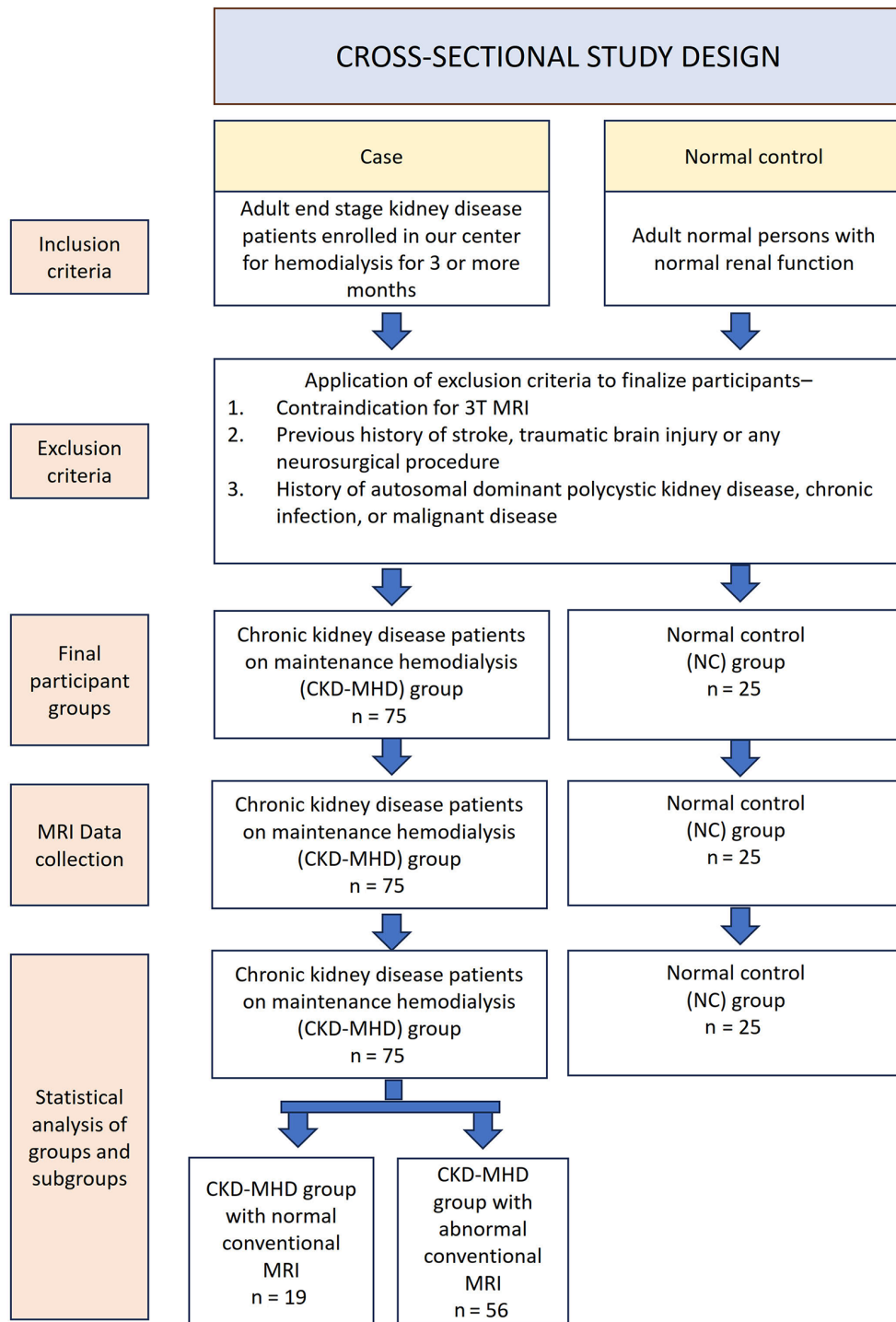


Figure 1. Flowchart illustrating the study design.

were corrected using the align option provided by the Syngo MR XA31 software. Subsequently, color-coded FA maps were created and fused with structural T1-weighted images (Figure 2). Volumes of interest were placed on these fusion images, centering on the anterior corona radiata, posterior corona radiata, genu of the corpus callosum, splenium of the corpus callosum, pons, and middle cerebellar peduncle using color-coding of fusion images (9) (Figure 3). Bilateral measurements were taken for the anterior and posterior corona radiata and middle cerebellar peduncles. Therefore, nine white matter tracts were evaluated in total. We reviewed slice-by-slice the FLAIR sequence and FA, ADC, AD, RD, and b0 maps, ensuring that VOIs were not placed on areas of artifact, white matter hyperintensity, SWI blooming, or lacunar infarct. Additionally, border areas such as those adjoining ventricles, partial volume effects, and neighboring tracts were avoided as much as possible. Two blinded radiologists independently calculated the DTI parameters for each acquisition to minimize researcher bias. Fractional anisotropy, MD, RD, and AD parameters were recorded for white matter fibers at a total of nine locations by each radiologist after averaging two readings.

### 3.6. Statistical Analysis

Demographic and patient characteristics for the CKD-MHD group and NC group were reported as means with standard deviations for quantitative variables and as percentages for categorical variables. Comparisons of DTI parameters between the CKD-MHD and NC groups were made using unpaired Student's *t*-tests after each variable was appropriately scaled so that each variable had unit variability. A significance level of  $P < 0.05$  was considered for comparison. However, Bonferroni correction was applied to account for multiple comparisons. Correlations between the DTI parameters for each location of the brain were calculated using the Pearson correlation coefficient.

Means, standard deviations, percentages, and intraclass correlation were calculated using Microsoft Excel for Microsoft 365 MSO (Version 2308 Build 16.0.16731.20052). All other statistical analyses were performed using R Statistical Software (version 4.12.0; R Foundation for Statistical Computing, Vienna, Austria).

## 4. Results

### 4.1. Demographic Results and Patient Characteristics

Our study included seventy-five patients in the CKD-MHD group and twenty-five controls in the NC group. The mean age was similar (42 years and 40 years for the CKD-MHD and NC groups, respectively), while the NC

group had more women (27% and 60% for the CKD-MHD and NC groups, respectively). The age distribution is depicted in Figure 4.

The mean dialysis vintage (time since initiation of hemodialysis) in the CKD-MHD group was 27 months, ranging from 3 months to 103 months.

### 4.2. Conventional MRI Findings

Thirteen patients (17%) within the CKD-MH group and 15 normal controls (60%) within the NC group had normal MRI brain features using the routine sequences. The prevalence of various MRI abnormalities in the two groups is depicted in Table 1.

**Table 1.** Prevalence of MRI Brain Features of Cerebral Small Vessel Disease in Chronic Kidney Disease-Maintenance Hemodialysis and NC Groups

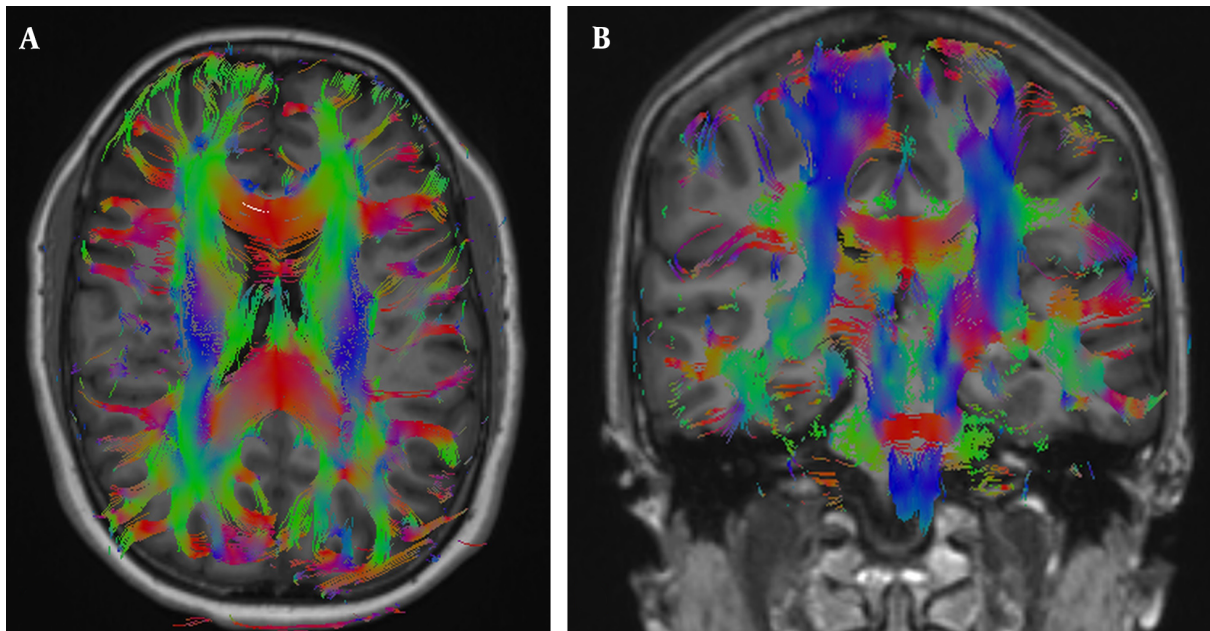
Parameters	CKD-MHD	NC
White matter hyperintensities	53 (70.6%)	8 (32%)
Microhemorrhages	11 (14.6)	0 (0%)
Lacunar infarcts	15 (20%)	2 (8%)
Brain atrophy	20 (26%)	5 (20%)

### 4.3. Comparison of DTI Parameters between CKD-MHD and NC

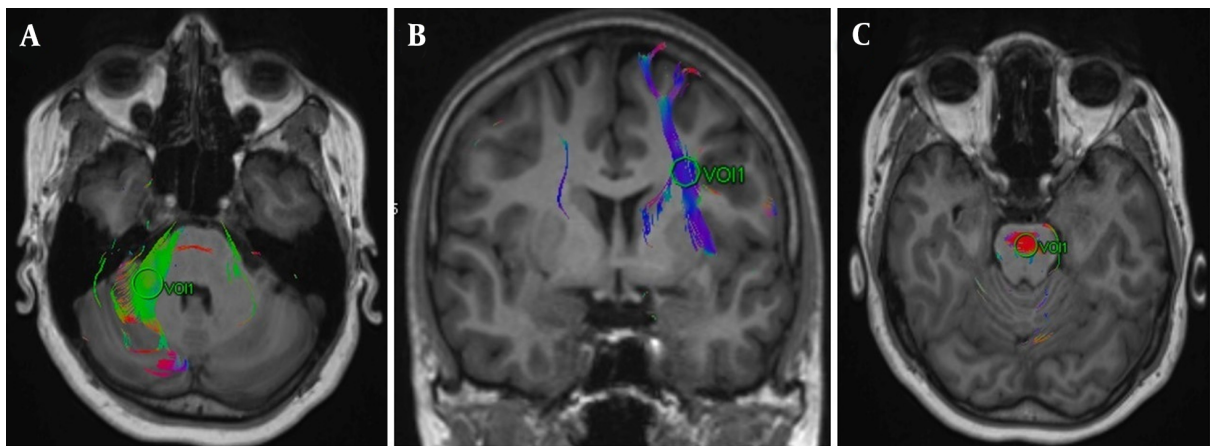
The four DTI parameters (FA, MD, RD, AD) were compared between CKD-MHD and NC groups at nine locations of the brain - right anterior corona radiata (RACR), corpus callosum genu (CCG), left anterior corona radiata (LACR), right posterior corona radiata (RPCR), corpus callosum splenium (CCS), left posterior corona radiata (LPCR), transverse pontine fibers (TP), right middle cerebellar peduncle (RMCP), left middle cerebellar peduncle (LMCP). Fractional anisotropy was significantly decreased at CCG, RACR, and LACR. MD was significantly increased at CCG, CCS, RACR, LACR, RPCR, LPCR, and LMCP. Radial diffusivity was significantly increased at CCG, CCS, RACR, LACR, RPCR, and LPCR. AD was significantly increased at CCS and LPCR. The results of these 36 comparisons with their statistical significance after Bonferroni correction are depicted in Tables 2, 3, and 4.

### 4.4. Comparison of DTI Parameters between CKD-MHD and NC When Conventional MRI is Normal

There was no statistically significant difference among the DTI parameters of CKD-MHD and NC groups for the subset of cases where conventional MRI was normal. The results of these 36 comparisons after the Bonferroni correction are depicted in Appendix 1.



**Figure 2.** Image showing color-coded fractional anisotropy (FA) maps fused with structural T1-weighted images. A, axial fused image; B, coronal fused image.



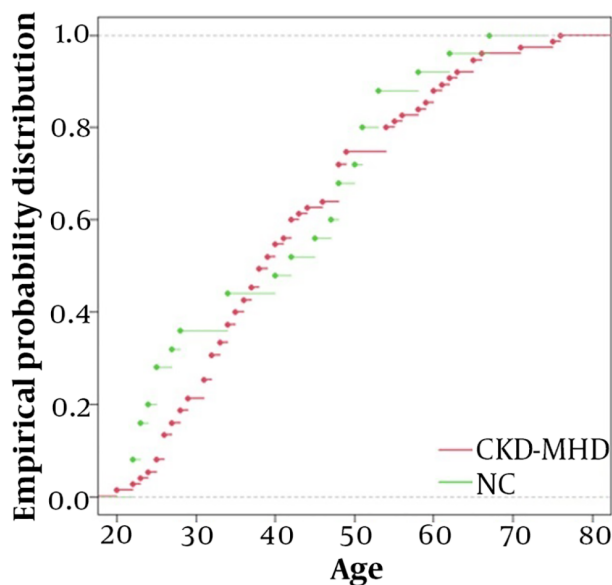
**Figure 3.** Figure showing volumes of interest (VOI) placed on A, the right cerebellar peduncle; B, the left anterior corona radiata; and C, transverse pontine fibers. In the VOI approach for diffusion tensor imaging (DTI) estimation, the DTI parameters of white matter tracts are computed using circular regions known as Volumes of Interest, which are designated by the MRI operator to pinpoint and localize these specific white matter tracts.

#### 4.5. Comparison of DTI Parameters Between CKD-MHD and NC When Conventional MRI is Abnormal

Significant statistical differences were observed between the DTI parameters of CKD-MHD and NC groups for the subset of cases where conventional MRI was abnormal. The results of these comparisons are shown in Appendix 2.

#### 4.6. Correlation of DTI Parameters with Each Other in Specific Locations and Between Various Locations

Pearson's correlation coefficient was calculated between the four DTI parameters (FA, MD, RD, AD) in the nine areas of the brain - RACR, CCG, LACR, RPCR, CCS, LPCR, TP, RMCP, LMCP. The results are depicted in heat maps separately for both CKD-MHD and NC groups in Figure 5. It is observed that correlations among different locations are stronger among controls (NC group) compared to



Age	Mean	Median	SD
CKD-MHD	41.89	39	13.82
NC	40.08	42	14.08

**Figure 4.** Empirical probability distribution graph showing age distributions in chronic kidney disease (CKD)-maintenance hemodialysis (MHD) (red) and NC (green) groups appear to be similar. Similar age distribution in case and control suggests age is not a confounder in our study.

**Table 2.** Comparison Results of Diffusion Tensor Imaging Parameters Between Chronic Kidney Disease-Maintenance Hemodialysis and NC Groups in Anterior Cerebral Hemispheres

DTI Parameter	Scaled Mean NC	Scaled Mean CKD-MHD	Difference in Scaled Mean	P-Value	Significance After Bonferroni Correction
CCG FA	1.08022425	0.958506638	Decreased	3.57E-08	Significant
CCG MD	0.95787717	1.003936461	Increased	0.00025827	Significant
CCG RD	0.89343578	1.017975314	Increased	5.29E-07	Significant
CCG AD	0.9964807	0.992460603	Decreased	0.74233652	Not significant
RACR FA	1.05372518	0.964508917	Decreased	0.001007518	Significant
RACR MD	0.94866917	1.006305887	Increased	9.99E-05	Significant
RACR RD	0.91634818	1.01064799	Increased	0.000216952	Significant
RACR AD	0.96551552	1.002088074	Increased	0.011297148	Not significant
LACR FA	1.08059666	0.949367977	Decreased	4.50E-06	Significant
LACR MD	0.93965054	1.00855825	Increased	0.000136995	Significant
LACR RD	0.87860948	1.017876254	Increased	9.83E-06	Significant
LACR AD	0.96051414	1.003695146	Increased	0.003252213	Not significant

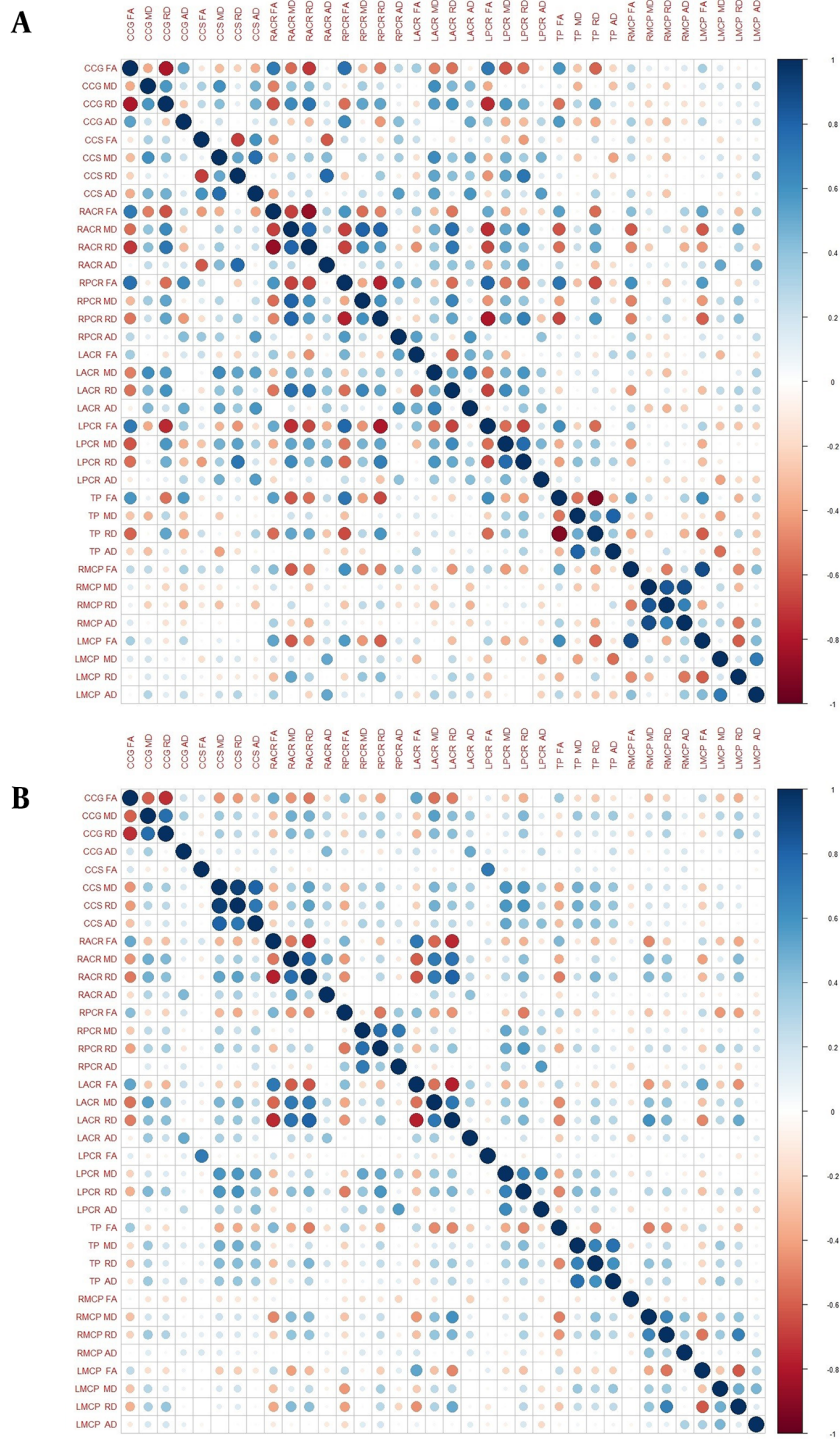
Abbreviations: CKD-MHD, chronic kidney disease-maintenance hemodialysis; DTI, diffusion tensor imaging; RACR, right anterior corona radiate; CCG, corpus callosum genu; LACR, left anterior corona radiate; FA, fractional anisotropy; MD, mean diffusivity; RD, radial diffusivity; AD, axial diffusivity.

hemodialysis patients (CKD-MHD group).

Fractional anisotropy and RD are highly and negatively correlated ( $R = -0.7904$ ,  $P = 0.00001$ ) in anterior locations where FA has significantly decreased in the CKD-MHD group (CCG, RACR, LACR). In posterior locations of the brain (CCS, LPCR) where AD has significantly increased, AD and MD are strongly positively correlated ( $R = 0.7734$ ,  $P = 0.00001$ ).

#### 4.7. Intraclass Correlations Between DTI Parameters Obtained by Two Radiologists

The intraclass correlation coefficients (ICCs) were very high for FA (CKD-MHD: 0.85 and NC: 0.89), high for MD (CKD-MHD: 0.84 and NC: 0.87), RD (CKD-MHD: 0.78 and NC: 0.85), and AD (CKD-MHD: 0.80 and NC: 0.82) (Appendix 3).



**Figure 5.** Correlation heat map for diffusion tensor imaging (DTI) parameters. A, correlation between DTI parameters in NC group; B, correlation between DTI parameters in chronic kidney disease (CKD)-maintenance hemodialysis (MHD) group.

**Table 3.** Comparison Results of Diffusion Tensor Imaging Parameters Between Chronic Kidney Disease-Maintenance Hemodialysis and NC Groups in Posterior Cerebral Hemispheres

DTI Parameter	Scaled Mean NC	Scaled Mean CKD-MHD	Difference in Scaled Mean	P-Value	Significance After Bonferroni Correction
CCS FA	0.00188728	0.134446406	Increased	0.32086503	Not significant
CCS MD	0.88767887	1.016730977	Increased	1.22E-08	Significant
CCS RD	0.87316532	1.010249293	Increased	8.79E-06	Significant
CCS AD	0.9119682	1.014057591	Increased	1.08E-06	Significant
RPCR FA	1.02686276	0.973774522	Decreased	0.034476347	Not significant
RPCR MD	0.92644725	1.012485469	Increased	1.37E-07	Significant
RPCR RD	0.91744416	1.011856755	Increased	0.000146352	Significant
RPCR AD	0.95068874	1.003001774	Increased	0.003857807	Not significant
LPCR FA	0.00068067	0.188272121	Increased	0.158703772	Not significant
LPCR MD	0.90871853	1.015353862	Increased	6.72E-07	Significant
LPCR RD	0.92239235	1.009645682	Increased	9.35E-05	Significant
LPCR AD	0.92000966	1.011490851	Increased	2.44E-06	Significant

Abbreviations: CKD-MHD, chronic kidney disease-maintenance hemodialysis; DTI, diffusion tensor imaging; RPCR, right posterior corona radiate; CCS, corpus callosum splenium; LPCR, left posterior corona radiate; FA, fractional anisotropy; MD, mean diffusivity; RD, radial diffusivity; AD, axial diffusivity.

**Table 4.** Comparison Results of Diffusion Tensor Imaging Parameters Between Chronic Kidney Disease-Maintenance Hemodialysis and NC Groups in Brainstem and Cerebellar Hemispheres

DTI Parameter	Scaled Mean NC	Scaled Mean CKD-MHD	Difference in Scaled Mean	P Value	Significance After Bonferroni Correction
TP FA	1.03934422	0.97407626	Decreased	0.002346215	Not significant
TP MD	0.97495922	0.996296709	Increased	0.237357769	Not significant
TP RD	0.92252514	1.005991699	Increased	0.007627487	Not significant
TP AD	0.98404665	0.995017071	Increased	0.398248839	Not significant
RMCP FA	0.00069632	0.187297211	Increased	0.160943988	Not significant
RMCP MD	0.95877764	1.001076648	Increased	0.046995326	Not significant
RMCP RD	0.97534909	0.990321555	Increased	0.58764979	Not significant
RMCP AD	1.00009128	0.989641009	Decreased	0.563599048	Not significant
LMCP FA	1.0302902	0.97420812	Decreased	0.014112099	Not significant
LMCP MD	0.94939491	1.005145211	Increased	0.000576917	Significant
LMCP RD	0.94035147	1.005280504	Increased	0.007242027	Not significant
LMCP AD	0.97260608	0.999533158	Increased	0.115924825	Not Significant

Abbreviations: CKD-MHD, chronic kidney disease-maintenance hemodialysis; DTI, diffusion tensor imaging; TP, transverse pontine fibres; RMCP, right middle cerebellar peduncle; LMCP, left middle cerebellar peduncle; FA, fractional anisotropy; MD, mean diffusivity; RD, radial diffusivity; AD, axial diffusivity.

## 5. Discussion

### 5.1. Significant Differences in DTI Parameters in CKD-MHD Population

In six out of the nine investigated white matter tracts, two or more DTI parameters exhibited significant differences after Bonferroni correction between the CKD-MHD and NC groups. However, when comparing the same DTI parameters between these groups in cases where routine brain MRI yielded normal results, none

of the DTI parameters showed significant differences after Bonferroni correction. Previous studies have demonstrated that DTI parameters can detect the loss of white matter structural integrity in the brain (13-16). However, our study contributes by highlighting that in patients with chronic kidney disease undergoing hemodialysis, if a routine brain MRI scan is normal, then there are no significant differences in DTI parameters compared with normal.



### 5.2. Physiological and Pathological Correlation of the Diffusion Parameters

Correlation studies involving mouse models, examining the relationship between radiology and histology, have shown that radial diffusivity correlates with demyelination, indicating an increase in the loss of myelin (17, 18). Conversely, axial diffusivity is associated with axonal damage in animal models to varying degrees (19).

In our study, we found a strong negative correlation between FA and RD in the CKD-MHD group in anterior locations (RACR, LACR, CCG), where FA is significantly decreased. In these locations, AD has not significantly changed, and its correlation with other DTI parameters is poor. Given the established association of radial diffusivity with demyelination, our findings support the hypothesis that demyelination likely underlies the compromised white matter integrity observed in chronic kidney disease patients undergoing maintenance hemodialysis, particularly in the anterior regions of the brain.

In two posterior locations (CCS, LPCR) in our study, there was a significant increase in axial diffusivity in the CKD-MHD group compared to the NC group. In these locations, FA was neither significantly increased nor correlated with other DTI parameters. However, increased AD in these locations positively correlated with both MD and RD, which were significantly increased. Therefore, our study indicates a variance in the pathogenesis of white matter tracts between anterior and posterior locations. This is consistent with prior research that has identified differences in DTI parameters among white matter fibers situated in the anterior and posterior regions of the brain (7, 20).

### 5.3. Intraclass Correlations between DTI Parameters Obtained by Two Radiologists

Tract-based spatial statistics is the most advanced technique for calculating DTI parameters, preferred over the VOI method due to its high sensitivity, objectivity, and interpretability in the analysis of multi-patient diffusion studies. However, the VOI method offers two notable advantages over TBSS. Firstly, it can be used in the majority of MRI centers with readily available, commercially approved software, without requiring advanced programming or statistical expertise from the user. Secondly, unlike TBSS, the VOI method allows for the calculation of DTI parameters for individual patients rather than necessitating a group of patients.

Although the VOI method is observer-dependent, our study demonstrates high interobserver agreement for all DTI parameters (FA, MD, RD, AD). This finding aligns

with previous observations of adequate inter-observer repeatability using the quantitative freehand method for calculating DTI parameters (9).

### 5.4. Limitations

Our study has a few limitations. Firstly, our study design precludes us from making interpretations about whether hemodialysis or other potential confounding risk factors linked to chronic kidney disease are responsible for these changes in DTI parameters. Secondly, our study lacks the ability to determine the prevalence of these DTI changes in individuals with mild and severe chronic kidney disease who are not undergoing dialysis. Thirdly, as a single-center study utilizing a single MRI vendor software, our research does not address the potential inter-vendor variability in the calculation of DTI parameters.

### 5.5. Conclusions

In our study on the Indian population of chronic kidney disease patients undergoing maintenance hemodialysis, we observed significant differences in certain DTI parameters across widespread white matter tracts of the brain using the VOI method, with an acceptable to excellent interobserver agreement. However, when compared to individuals with normal renal function, we were unable to detect any significant alterations in DTI brain parameters within a subgroup of hemodialysis patients whose routine brain MRI results were normal. The outcomes of our study suggest opportunities for future research to explore the onset of DTI changes in the natural progression of chronic kidney disease using the same VOI method. Longitudinal studies may be conducted involving various cohorts of CKD patients in different stages of the disease and in post-transplant CKD patients to understand if white matter changes begin early in CKD, progress with declining eGFR, and potentially reverse after renal transplantation. Our study also calls for future studies aiming to establish DTI as a diagnostic investigation using the VOI method. Multicenter studies involving different commercial MRI vendor software are essential for conducting receiver operating characteristic analysis to determine the normal range of DTI parameters and establish vendor-independent cutoff values for diagnosing CSVD. After classifying CKD patients based on DTI into those with or without CSVD, these patients may be followed to develop a model for stratifying the risk of stroke in CKD patients based on DTI values.

## Supplementary Material

Supplementary material(s) is available here [To read supplementary materials, please refer to the journal website and open PDF/HTML].

## Acknowledgments

We acknowledge Prof. Radhendushka Srivastava's assistance in statistical analysis and Dr. Samrat Mandal's contribution to preparing the manuscript. We have not received any external funding for this work.

## Footnotes

**Authors' Contribution:** Study concept and design, drafting of the manuscript, and critical revision of the manuscript: T. A. D., T. K., R. K., D. S., N. S., P. W., C. B., and A. S.; acquisition of data, analysis and interpretation of data, and study supervision: T. A. D., T. K., R. K., and D. S.; statistical analysis: D. S., N. S., P. W., C. B., and A. S.; administrative, technical, and material support: R. K., D. S., N. S., P. W., C. B., and A. S. All authors read and approved the final manuscript.

**Conflict of Interests:** The authors declare no conflict of interest, financially or non-financially. All authors are employees of Dr. D. Y. Patil Medical College Hospital & Research Centre and are not funded by any external research support. They receive salaries from Dr. D. Y. Patil Medical College Hospital & Research Centre. None of the authors have personal financial interests, related stocks or shares in companies, related patents. None of them are editorial board members or reviewers of this journal.

**Data Availability:** The dataset presented in the study is available upon request from the corresponding author during submission or after publication. The data are not publicly available due to patient privacy.

**Ethical Approval:** The protocols of this research were evaluated and confirmed by the Institutional Ethics Sub-Committee of Dr. D. Y. Patil Vidyapeeth University, Pune, India, via order number IESC/S.SP/2019/02 dated 25.05.21.

**Funding/Support:** We have not received any external funding support for this work.

**Informed Consent:** The research objectives and process were explained to the subjects, and written informed consent was obtained from them in their native language.

## References

- Kovesdy CP. Epidemiology of chronic kidney disease: an update 2022. *Kidney Int Suppl* (2011). 2022;**12**(1):7-11. [PubMed ID: 35529086]. [PubMed Central ID: PMC9073222]. <https://doi.org/10.1016/j.kisu.2021.11.003>.
- Chojdak-Lukasiewicz J, Dziadkowiak E, Zimny A, Paradowski B. Cerebral small vessel disease: A review. *Adv Clin Exp Med*. 2021;**30**(3):349-56. [PubMed ID: 33768739]. <https://doi.org/10.17219/acem/131216>.
- Ranzenberger LR, M Das J, Snyder T. Diffusion Tensor Imaging. *StatPearls [Internet]*. Treasure Island, FL: StatPearls Publishing; 2024.
- Scheppach JB, Wu A, Gottesman RF, Mosley TH, Arsiwala-Scheppach IT, Knopman DS, et al. Association of Kidney Function Measures With Signs of Neurodegeneration and Small Vessel Disease on Brain Magnetic Resonance Imaging: The Atherosclerosis Risk in Communities (ARIC) Study. *Am J Kidney Dis*. 2023;**81**(3):261-269 e1. [PubMed ID: 36179945]. [PubMed Central ID: PMC9974563]. <https://doi.org/10.1053/j.ajkd.2022.07.013>.
- Chen HJ, Qiu J, Xu X, Guo Y, Fu L, Fu Q, et al. Abnormal white matter along fibers by automated fiber quantification in patients undergoing hemodialysis. *Neurol Sci*. 2023;**44**(12):4499-509. [PubMed ID: 37393206]. <https://doi.org/10.1007/s10072-023-06912-8>.
- Vemuri P, Davey C, Johansen KL, Zuk SM, Reid RI, Thostenson KB, et al. Chronic Kidney Disease Associated with Worsening White Matter Disease and Ventricular Enlargement. *J Alzheimers Dis*. 2021;**83**(4):1729-40. [PubMed ID: 34459402]. [PubMed Central ID: PMC8609691]. <https://doi.org/10.3233/JAD-210604>.
- Chou MC, Hsieh TJ, Lin YL, Hsieh YT, Li WZ, Chang JM, et al. Widespread white matter alterations in patients with end-stage renal disease: a voxelwise diffusion tensor imaging study. *AJNR Am J Neuroradiol*. 2013;**34**(10):1945-51. [PubMed ID: 23788598]. [PubMed Central ID: PMC7965420]. <https://doi.org/10.3174/ajnr.A3511>.
- Zhang C, Yu H, Cai Y, Wu N, Liang S, Zhang C, et al. Diffusion tensor imaging of the brain white matter microstructure in patients with chronic kidney disease and its correlation with cognition. *Front Neurol*. 2022;**13**:1086772. [PubMed ID: 36588888]. [PubMed Central ID: PMC9798235]. <https://doi.org/10.3389/fneur.2022.1086772>.
- Hakulinen U, Brander A, Ilvesmaki T, Helminen M, Ohman J, Luoto TM, et al. Reliability of the freehand region-of-interest method in quantitative cerebral diffusion tensor imaging. *BMC Med Imaging*. 2021;**21**(1):144. [PubMed ID: 34607554]. [PubMed Central ID: PMC8491381]. <https://doi.org/10.1186/s12880-021-00663-8>.
- Markus HS, de Leeuw FE. Cerebral small vessel disease: Recent advances and future directions. *Int J Stroke*. 2023;**18**(1):4-14. [PubMed ID: 36575578]. [PubMed Central ID: PMC9806465]. <https://doi.org/10.1177/17474930221144911>.
- da Silva PHR, Paschoal AM, Secchinatto KF, Zotin MCZ, Dos Santos AC, Viswanathan A, et al. Contrast agent-free state-of-the-art magnetic resonance imaging on cerebral small vessel disease - Part 2: Diffusion tensor imaging and functional magnetic resonance imaging. *NMR Biomed*. 2022;**35**(8). e4743. [PubMed ID: 35429070]. <https://doi.org/10.1002/nbm.4743>.
- Egle M, Hilal S, Tuladhar AM, Pirpamer L, Bell S, Hofer E, et al. Determining the OPTIMAL DTI analysis method for application in cerebral small vessel disease. *Neuroimage Clin*. 2022;**35**:103114. [PubMed ID: 35908307]. [PubMed Central ID: PMC9421487]. <https://doi.org/10.1016/j.nicl.2022.103114>.
- Liu Y, Jiang Y, Du W, Gao B, Gao J, Hu S, et al. White matter microstructure alterations in type 2 diabetes mellitus and its correlation with cerebral small vessel disease and cognitive performance. *Sci Rep*. 2024;**14**(1):270. [PubMed ID: 38167604]. [PubMed Central ID: PMC10762026]. <https://doi.org/10.1038/s41598-023-50768-z>.
- Carbone C, Balboni E, Beltrami D, Gasparini F, Vinceti G, Galligani C, et al. Neuroanatomical Correlates of Cognitive Tests in Young-onset MCI. *J Integr Neurosci*. 2023;**22**(6):152. [PubMed ID: 38176949]. <https://doi.org/10.31083/j.jin2206152>.

15. Lijdsman S, Oostrom KJ, van Sandwijk MS, Bouts AH, van Hoeck K, de Jong H, et al. Risk factors for neurocognitive impairment and the relation with structural brain abnormality in children and young adults with severe chronic kidney disease. *Pediatr Nephrol.* 2023;**38**(6):1957-69. [PubMed ID: 36322259]. [PubMed Central ID: PMC10154258]. <https://doi.org/10.1007/s00467-022-05781-1>.
16. Lijdsman S, Konigs M, van Sandwijk MS, Bouts AH, van Hoeck K, de Jong H, et al. Structural brain abnormalities in children and young adults with severe chronic kidney disease. *Pediatr Nephrol.* 2022;**37**(5):1125-36. [PubMed ID: 34800137]. [PubMed Central ID: PMC9023396]. <https://doi.org/10.1007/s00467-021-05276-5>.
17. Althobity AA, Khan N, Sandrock CJ, Woodruff TM, Cowin GJ, Brereton IM, et al. Multiparametric magnetic resonance imaging for detection of pathological changes in the central nervous system of a mouse model of multiple sclerosis in vivo. *NMR Biomed.* 2023;**36**(10). e4964. [PubMed ID: 37122101]. [PubMed Central ID: PMC10909458]. <https://doi.org/10.1002/nbm.4964>.
18. Galbusera R, Bahn E, Weigel M, Schaedelin S, Franz J, Lu PJ, et al. Postmortem quantitative MRI disentangles histological lesion types in multiple sclerosis. *Brain Pathol.* 2023;**33**(6). e13136. [PubMed ID: 36480267]. [PubMed Central ID: PMC10580009]. <https://doi.org/10.1111/bpa.13136>.
19. Kopanitsa MV, Lehtimäki KK, Forsman M, Suhonen A, Koponen J, Piipponiemi TO, et al. Cognitive disturbances in the cuprizone model of multiple sclerosis. *Genes Brain Behav.* 2021;**20**(1). e12663. [PubMed ID: 32372528]. <https://doi.org/10.1111/gbb.12663>.
20. Jiang Y, Gao Q, Liu Y, Gao B, Che Y, Lin L, et al. Reduced White Matter Integrity in Patients With End-Stage and Non-end-Stage Chronic Kidney Disease: A Tract-Based Spatial Statistics Study. *Front Hum Neurosci.* 2021;**15**:774236. [PubMed ID: 34955791]. [PubMed Central ID: PMC8709581]. <https://doi.org/10.3389/fnhum.2021.774236>.