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A DEEP LEARNING-BASED CAD SYSTEM FOR RENAL ALLOGRAFT ASSESSMENT: DIFFUSION, BOLD, AND CLINICAL BIOMARKERS

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Abstract

Recently, studies for non-invasive renal transplant evaluation have been explored to control allograft rejection. In this paper, a computer-aided diagnostic system has been developed to accommodate with an early-stage renal transplant status assessment, called RT-CAD. Our model of this system integrated multiple sources for a more accurate diagnosis: two image-based sources and two clinical-based sources. The image-based sources included apparent diffusion coefficients (ADCs) and the amount of deoxygenated hemoglobin ($R2^*$). More specifically, these ADCs were extracted from 47 diffusion weighted magnetic resonance imaging (DW-MRI) scans at 11 different b -values (b_0 , b_{50} , b_{100} , ..., b_{1000} s/mm²), while the $R2^*$ values were extracted from 30 blood oxygen level-dependent MRI (BOLD-MRI) scans at 5 different echo times (2ms, 7ms, 12ms, 17ms, and 22ms). The clinical sources included serum creatinine (SCr) and creatinine clearance (CrCl). First, the kidney was segmented through the RT-CAD system using a geometric deformable model called a level-set method. Second, both ADCs and $R2^*$ were estimated for common patients ($N = 30$) and then were integrated with the corresponding SCr and CrCl. Last, these integrated biomarkers were considered the discriminatory features to be used as trainers and testers for future deep learning-based classifiers such as stacked auto-encoders (SAEs). We used a k -fold cross-validation criteria to evaluate the RT-CAD system diagnostic performance, which achieved the following scores: 93.3%, 90.0%, and 95.0% in terms of accuracy, sensitivity, and specificity in differentiating between acute renal rejection (AR) and non-rejection (NR). The reliability and completeness of the RT-CAD system was further accepted by the area under the curve score of 0.92. The conclusions ensured that the presented RT-CAD system has a high reliability to diagnose the status of the renal transplant in a non-invasive way.

Index Terms—

RT-CAD; DW-MRI; BOLD-MRI; SAEs

1. INTRODUCTION

More than 15% of the American people suffer from chronic kidney disease (CKD) as it is namely the ninth leading cause of death in the USA. Additionally, more than 700,000 of those patients are in the last stage of CKD where the kidney loses its function over time resulting in end-stage renal disease (ESRD). As a result, more than \$114 billion is used as annual expenses to treat and diagnose ESRD and CKD [1]. Renal transplantation is considered the most effective solution for ESRD patients. However, finding a suitable donor can be complicated and difficult. Consequentially, there are only about 17,500 annual renal transplantation operations. Additionally, these transplants may lead to renal allograft rejection or allograft dysfunction in the first 5 years post-transplantation within 15%–27% of the patients. To avoid such complications, precautions such as early diagnosis and treatment plans can be taken during the early stages to minimize permanent damage or failure of the renal transplantation [2, 3]. Due to the lack of kidney donors, alive or not, routine clinical follow-ups, estimation, and correct evaluation of the renal transplant is essential to curtail loss of allograft [4, 5].

With the approval by the National Kidney Foundation (NKF), glomerular filtration rate (GFR) is the most recommended diagnostic tool to indicate the overall function of the graft post-transplantation. However, this GFR method is less sensitive and considered a late biomarker for graft dysfunction (i.e., noticeable observation only after 60% of the renal allograft function is lost) [6]. If the glomerular filtration rate results are irregular, needle biopsy is used as the compelling acute rejection (AR) diagnostic tool. Though biopsy is the gold standard method, it is not favorable because it is extremely invasive, time consuming, expensive, and frequently causes injurious events such as bleeding, inflections, and more. Therefore, a non-invasive alternative that has the ability to provide early and accurate diagnosis of AR is crucial to fulfil the unmet clinical need.

As alternatives, many medical imaging approaches implied a higher accuracy to diagnose renal dysfunction as well as its cause. Two methods that are commonly used to determine the renal transplant status during the early stage after transplantation are diffusion-weighted magnetic resonance imaging (DW-MRI) [7–11] and blood oxygen level-dependent imaging (BOLD-MRI) [8, 12–19]. These methods are advantageous because they provide information about the anatomy and function of the soft tissue being detected such as kidneys. Another advantage is that they both avert the use of contrast agents due to the possibility of their toxicity, especially if the GFR demonstrates a value under 30 ml/min [20]. One of many who tested DW-MRI's assessment on renal function is Eisenberger et al. [11]. Each scan had 10 different b -values for each of the 15 patients with renal allografts. It resulted in 10 non-rejection (NR), 4 AR, and 1 acute tubular necrosis (ATN). From all the b -values, ADC's mean and standard deviation values were estimated after placing manual region of interests (ROIs). For the 10 NR patients, significantly higher ADC values were presented in the cortex and the medulla than AR and the ATN groups. Each ADC value correlates with the creatinine levels. Hueper et al. [7] administered a study where DW-MRI scans of 64 participants were collected at b_0 and b_{600} s/mm². Out of the 64 patients, 33 were NR and the remaining 31 were AR with a major decrease in their ADC values.

As for studies on BOLD-MRI, Djamali et al. [14] estimated the amount of deoxygenated hemoglobin to detect early stage renal allograft dysfunction. Out of 23 renal allografts, 5 of which were NR, 13 were AR, and 5 were ATN, the AR allografts granted the lowest both medullary amount of deoxygenated hemoglobin ($R2^*$) values and medullary to cortical $R2^*$ ratios. Furthermore, an expanded application of this experiment was conducted by Han et al. [12]. This study contained 110 renal allograft patients with 82 NR, 21 AR, and 7 ATN. Results of this study suggest higher mean $R2^*$ values in cortices and medullas of ATN patients in comparison to AR and NR patients. However, higher mean cortical $R2^*$ values were presented in NR patients compared to AR patients. In this study though, there was no direct relationship between creatinine levels and $R2^*$ values.

Besides these studies, many others have utilized both DW-MRI and BOLD-MRI to examine kidneys post-transplantation [8, 21]. For example, Vermathen et al. [21] routinely checked nine patients post transplantation for three years in row. Each of the nine allografts underwent DW-MRI and BOLD-MRI twice. For NR allografts, minor and non-significant changes in functional parameters were indicated. For AR allografts though, ADC values were significantly decreased and $R2^*$ values were increased. Moreover, Liu et al. [8] also tested both models. Their experiment contained 50 renal allograft patients, 10 of which were AR, 35 were NR, and 5 were ATN. Similarly to the previous studies, ADC values were significantly reduced for AR patients and medullary $R2^*$ values were higher for ATN patients in comparison to NR and AR patients.

Although these studies were significant and resourceful, they were also constrained by some limitations. Firstly, the kidney was vulnerable to error, delineation, and time given that 2D ROIs were being placed. Secondly, significant reports were only presented when studying groups with different renal allograft status. Lastly, these studies represented certain MRI modalities. Neither of the studies combined diverse MRI modalities with clinical biomarkers for an inclusive, computer-aided diagnostic system for early stage AR identification. To compensate for these lacks, a novel fully automated computer-aided diagnostic system to accurately assess AR at an early stage post-transplantation, (RT-CAD), is developed. A visual of this model is presented in Fig. 1.

2. METHODS

A precise RT-CAD framework, (Fig. 1), to assess renal transplant status was developed. The RT-CAD system contains certain steps to receive the final assessment: (1) the kidney is automatically segmented from the surrounding tissue using DW-MRI scans as well as BOLD-MRI scans; (2) extraction/construction of cumulative distribution functions (CDFs) using voxel-wise ADC maps and $R2^*$ values from the segmented kidney. DW-MRI scans are captured under different b -values and BOLD-MRI scans are captured at different echo-times as well at two different geographical ranges; (3) the extracted multimodal image markers are then combined/integrated with both SCr and CrCl clinical biomarkers; and (4) placing those integrated biomarkers into the newly developed deep learning classification model, using stacked auto-encoders (SAEs), to diagnose the renal allograft as AR or NR. Further details on this framework will be discussed in the next few subsections.

2.1. Kidney Segmentation

Precise feature extraction and diagnosis essentially require an automated and accurate segmentation of kidneys. preprocessing the data before administering our previously developed segmentation system was performed [22, 23] to enhance the segmentation accuracy. An intensity histogram equalization was used to reduce both noise effect and the image heterogeneities on the bias-corrected MR images. As for the kidney motions, non-rigid registration of B-splines [24] was applied to decrease the variability of the given subjects. Next, we employed level-sets to obtain the kidney segmentation in a 3D manner [22]. For a precise kidney segmentation analysis, a guiding force, that includes local appearance, shape, and spatial MRI features was placed in the regional statistics which came from the kidney as well as the background regions. Those features were merged using a joint Markov-Gibbs random field (MGRF) image model. For further detail of this approach, please view Shehata et al. [22].

2.2. Feature Extraction

2.2.1. Diffusion Weighted Image Markers: The movement of water molecules depends on the structure and function of designated tissue. The kidney normally diffuses water in the nephrons. If the tissue has a compulsive condition, it is more likely to have unusual diffusion patterns. DW-MRI represents the tissue function into images through the amount of water dispersed [8, 25–27]. Post-segmentation of the kidney, the voxel-wise ADCs are calculated accurately as follows [28–30]:

$$ADC_{vx} = \frac{\ln(g_{0:vx} - g_{b:vx})}{b}, \quad (1)$$

where $\mathbf{vx}$ is a voxel with its 3D Cartesian location (x, y, z) , g_0 denotes the grey value of the segmented image at b_0 , and g_b denotes the grey value of the segmented image at a given b -value.

As stated, the equation allows the estimation of voxel-wise ADCs which were later on used as distinguishing features to determine the status of the renal transplant. Although, there are possible limitations with this method. One of the limitations occurs with the possible need of efficient amount of classification time and training when there is a large amount of data. Another possible limitation occurs when there is a diverse data size. The data then might trun-cate or have padding dilemmas. To defeat these limitations, we used the cumulative distribution functions (CDFs) of those ADCs at the 11 different b -values. However, in order to establish these CDFs, the maximum and minimum values of the ADCs were determined for the diverse data. Subsequently, the CDFs were also obtained at 11 different b -values (100 steps for each CDF) resulting in a DW-MRI marker called (D_{mrks}) with a vector size of 1100×1 . A visual representation is shown in Fig. 2

2.2.2. BOLD-MR Image Markers: Using BOLD-MRI, one can measure the amount of oxygenated hemoglobin ($T2^*$) and take the reciprocal to estimate the amount of deoxygenated hemoglobin ($R2^*$) inside the renal allograft [19, 31]. In our case, the mean $R2^*$ values were calculated from the delineated renal allograft by the use of four different

echo-times (TEs) of 7, 12, 17, and 22 ms. The size of the resulted mean $R2^*$ vector was 4×1 (Fig. 3). This vector was then used as the BOLD-MRI markers (B_{mrks}) to identify renal allograft status. At 2ms, the BOLD-MRI is at its baseline ET; therefore, the pixel-wise $T2^*$ and $R2^*$ may be calculated as [18, 32]:

$$T2^*_{px} = \frac{t_0 - t}{\ln(SI_{t:px} - SI_{t_0:px})}, \quad (2)$$

$$R2^*_{px} = \frac{1}{T2^*_{px}}, \quad (3)$$

where px is a pixel with its 2D Cartesian location (x, y) , SI_{t_0} is the signal intensity of the segmented image at $ET = t$ ms, and SI_{t_0} is the signal intensity of the segmented image ET ($t_0 = 2$ ms).

2.3. Deep Learning: Stacked Autoencoders

Generally, there are many machine learning systems that are resourceful and reliable to detect certain diseases. Machine learning is one of the most beneficial and commonly used methods. To provide a better classification performance, an autoencoder (AE) is often used—an artificial neural network (ANN) that applies an unsupervised deep learning approach leading to a supervised backpropagation-based refinement algorithm [33–35]. Fig. 4, gives a visual of the main structure of an AE. Basically, an AE contains three layers: input, hidden, and output layers. The training process can be expressed by encoding and decoding where in encoding the input data is arranged through the hidden layer and in decoding the input data is regenerated back from the hidden representation. Both of these processes however are mainly utilized to provide an estimation to the identity function. The identity function suggests that the regenerated input or the output of the decoding process, $\hat{X}$, is essentially interchangeable to the input X . The essential goal is to force the AE to gain a abstract representation of the input, specifically when the input size is larger than the hidden nodes. Contrarily, the AE has to regenerate the input from the hidden features/activations.

Given the unlabeled training input dataset $\{X_n\}_{n=1}^N$, such that $X_n \in \mathbb{R}^m$ (real numbers) and H_n imitates the covert layer's features eventuating from the encoding process of input vector X_n . The following equation demonstrates the encoding process:

$$H_n = f_e(W_e X_n + B_e), \quad (4)$$

where f_e serves as the encoding function. Specifically, in our framework, it is considered as a sigmoid function or a differential mono-tone scalar function with values pertaining from 0 and 1. Weight matrix and the bias vector are represented by W_e and B_e , respectively. Additionally, H_n can be constructed from the above-mentioned encoding process when the covert layer's features/activations are given. The decoding process to construct the regenerated input $\hat{X}$ is defined as:

$$\hat{X}_n = f_d(W_d H_n + B_d), \quad (5)$$

where f_d serves as the decoder function in the time that W_d and B_d represent the weights and biases of the decoder. To tune the optimal set of hyper-parameters of the AE, the reconstruction error is minimized as follows:

$$J_{AE}(W, B) = \frac{1}{2n} \sum_{i=1}^n \|\hat{X}_{W:i} - X_i\|^2, \quad (6)$$

where $\|\hat{X}_{W:i} - X_i\|^2$ denotes the loss function that needs to be reduced to minimize the reconstruction error $J_{AE}(W, B)$. As for the achievement of the ultimate SAEs, two AEs (AE_1 and AE_2) followed by a softmax classifier were trained and stacked together. This SAEs, Fig. 4, will ultimately be used in the RT-CAD for early identification of the AR renal allografts.

2.4. Classification using DW, BOLD, and Clinical Biomarkers

Multiple sources of information were obtained to achieve a precise renal transplant status determination. First, the constructed D_{mrks} vector of size 1100×1 to coordinate local blood diffusion characteristics and transplant status to one another. Second, the constructed B_{mrks} vector of size 4×1 to appraise how much deoxygenated hemoglobin content of the allograft is present and connecting it with the allograft status. Last, both clinical biomarkers (SCr and CrCl) were combined to produce C_{bmks} vector of size 2×1 , which sequentially gives a measurement of the creatinine levels of blood and urine and ultimately gives the quality of the filtration ability as well as transplant identification. Concatenation method was utilized to integrate these sources which culminated (I_{bmks}) as integrated biomarkers vector of size 1106×1 to be used as distinguishing features between AR and NR renal transplant patients.

After assimilating the I_{bmks} we used SAEs along with a leave-one-out cross-validation (LOOCV) method to achieve the final assessment. The I_{bmks} of size 1106×1 were fed as an input vector to SAEs to build our classification model. The cost function was then minimized as an optimization metric using a grid search algorithm for the acquisition of the optimal set of hyperparameters. Within the SAEs, the first layer had 9 nodes and the second hidden layer had 3 nodes, while the output softmax layer had 2 nodes. Additionally, it had weight decay parameter of 0.0022, weight of sparsity penalty term of 20, and desired average activation of the hidden units of 0.2421. Since this combination of hyperparameters provided the optimal, accurate, and resourceful diagnostic results using a LOOCV approach, they were accepted for the proposed RT-CAD system.

3. EXPERIMENTAL RESULTS

To prove the potential of the presented RT-CAD system, we evaluated the RT-CAD on various statistics attained from 47 patients after receiving their consents in the period between 2016 and 2019. All 47 patients underwent DW-MRI and renal biopsies. 30 of those patients underwent BOLD-MRI scans as well. Males were 31 and females were 16, ranging ages were 12–65 years with an average age of 35 ± 16.13 years. These data were

acquired from two geo-graphically different areas: USA and Egypt. DW-MRIs and biopsies assessed 30 patients as NR and 17 patients as AR renal allografts of which 20 NR patients and 10 AR patients underwent BOLD-MRI.

For all of the patients, routine assessment of laboratory values was obtained. SCr for the NR group had an average value of 1.19 ± 0.35 mg/dl. Additionally, CrCl for the NR group had an average value of 74.82 ± 26.25 ml/min. On the other hand, the SCr value for AR group had an average value of 1.62 ± 0.56 mg/dl and CrCl with an average value of 54.1 ± 22.30 ml/min. Table 1 summarizes the MRI data collection protocols. At increments of 100 s/mm², water signals were obtained from b_{100} – b_{1000} s/mm², as well as b_{50} and the baseline b_0 s/mm², for DW-MRI. As for BOLD-MRI, 5-various ETs were used (2, 7, 12, 17, 22 ms) to obtain the middle coronal image in each subject. The final assessment included results from biopsy, and both MRI scans. To ensure these results, the reports were verified by two physicians, a nephrologist and a radiologist.

Using the I_{bmrks} obtained for the 30 datasets that included both scans from both MR imaging modalities, the RT-CAD system was tested using a LOOCV approach. In other words, to determine the benefits of the integration of D_{mrks} with B_{mrks} and C_{bmrks} , an additional six tactics were completed using LOOCV method. The accuracy, sensitivity, specificity, and area under the curve (AUC) compared the results obtained from these schemes with those achieved by the RT-CAD system in Table 2. The first tactic (T_1), the D_{mrks} were utilized along with the same SAEs classifier. The second tactic (T_2), employed the B_{mrks} of size (i.e. 4×30) with a multi-layer perceptron ANN (MLP-ANN) classifier with two hidden layers ($hl_1 = 3$ nodes and $hl_2 = 1$ node). The third tactic (T_3) used the C_{bmrks} of size (i.e. 2×47), with a linear discriminant analysis (LDA) classifier. The fourth tactic (T_4) integrated both D_{mrks} with B_{mrks} resulting in DB_{mrks} . The fifth tactic (T_5) integrated both D_{mrks} with C_{bmrks} resulting in DC_{mrks} . The sixth tactic (T_6) integrated both B_{mrks} with C_{bmrks} resulting in BC_{mrks} . Table 2 concludes that using the I_{bmrks} increased the accuracy of the assessment. The reliability and completeness of the RT-CAD was supported by the highest AUC of 0.92.

4. CONCLUSIONS

To conclude, our work offers a new RT-CAD system that identify whether the renal transplant is AR or NR during early stages post-transplantation in a non-invasive way. In terms of accuracy, sensitivity, and specificity in differentiating between AR and NR, we used a k-fold cross-validation criteria system and scored 93.3%, 90.0%, and 95.0%, respectively. The robustness of the RT-CAD system was further accepted by the AUC value of 0.92. Our system includes various modalities: two clinical biomarkers and two imaging with DW-MRI and BOLD-MRI. RT-CAD is able to occupy multiple aspects of renal allograft dysfunction to ensure a more accurate assessment of renal allograft function. The completeness and reliability of the RT-CAD implies in its ability to function with missing data while still representing an accurate assessment. For further testing, a larger pool of patients utilizing both DW-MRI and BOLD-MRI would ensure the functionality of the RT-CAD. Additionally, various other markers (i.e. genomic and histopathology image markers) may be interspersed into the RT-CAD to augment its accuracy for AR identifications as well as further sub-types of AR identification for possible clinical treatments.

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Fig. 1.
The developed RT-CAD system to diagnose acute renal rejection post-transplantation at an early stage.

Fig. 2.

A visual representation of DW-MRI features estimation/construction. The ADCs are calculated from the previously segmented kidney at 11 various b -values. Subsequently, two estimations occur from the ADCs: PDFs (probability distribution functions) and cumulative distribution functions (CDFs) at all b -values.

Fig. 3.

The BOLD-MRI data, mean $R2^*$ values, are estimated at four echo-times of 7, 12, 17, 22 ms.

Fig. 4.

A stacked AE (SAE) can be constructed by stacking AE_1 with AE_2 and a softmax classifier. This is followed by a backpropagation technique to upgrade the hidden weights of the SAE.

Table 1.

Using 3T MRI Philips scanners in both USA and Egypt, MRI data were acquired using these acquisition protocols. Let TR/TE: repetition time/echo time, SZ: slice size, STH: slice thickness, FOV: field of view, NCs: number of cross-sections.

	MR Data Collection Parameters				
	TR/TE	SZ (<i>pixels</i>)	STH (<i>mm</i>)	FOV (<i>cm</i>)	NCs
Egypt (DW 30)	4400/82	176×176	4	22	24
USA (DW 17)	8000/93.7	256×256	4	36	38
Egypt (BOLD 30)	140/2	384×384	6	14.4	5

Table 2.

Summary of comparison of the ability to diagnose renal allograft status between RT-CAD using I_{bmrks} versus the six other tactics (T_1 , T_2 , T_3 , T_4 , T_5 , T_6). Here, accuracy is ACC, sensitivity is Sens, specificity is Spec, and area under the curve is AUC.

Tactic	Acc%	Sens%	Spec%	AUC
$T_1(D_{mrks})$	80.9	76.5	83.3	0.84
$T_2(B_{mrks})$	86.7	80.0	90.0	0.84
$T_3(C_{bmrks})$	70.2	80.0	52.9	0.71
$T_4(DB_{mrks})$	90.0	90.0	90.0	0.90
$T_5(DC_{mrks})$	87.2	82.4	90.0	0.88
$T_6(BC_{mrks})$	90.0	80.0	95.0	0.88
RT-CAD(I_{bmrks})	93.3	90.0	95.0	0.92