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Assessment of Dialysis Initiation by a Fuzzy mathematics Equation (ADIFE): a study protocol for a randomised controlled trial

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Abstract

Introduction Starting dialysis early and late results in a lower quality of life and a poor prognosis in hemodialysis patients. However, there remains no consensus on the optimal timing of dialysis initiation mainly due to the lack of suitable methods to assess variations in dialysis start times. We established a novel equation named DIFE (Dialysis Initiation based on Fuzzy-mathematics Equation) through a previous retrospective multicenter clinical cohort study in mainland China. The parameters of the DIFE include nine biochemical markers and clinical variables altogether influence dialysis initiation. To verify the external validity and clinical accuracy of DIFE, we

designed the ADIFE (assessment of DIFE) study with a prospective, multicenter, randomized controlled, open-label trial to assess the clinical outcomes between patients who initiate dialysis in an optimal start dialysis group and a late start dialysis group based on DIFE.

Methods and analysis A total of 496 enrolled end-stage renal disease (ESRD) subjects will be randomised 1:1 to the optimal start dailysis group with DIFE value between 30 and 35 or late start dailysis group with DIFE value less than 30 using the Randomization and Trial Supply Management (RTSM) system. Participants will be assessed with signs and symptoms change, dialysis mode and parameters, biochemical and inflammatory markers, Subjective Global Assessment (SGA), Kidney Disease Quality of Life Short Form (KDQOL-SF^{TM}), Cognitive Assessment (MoCA), Medical costs, adverse events, and concomitant medication at baseline, pre-dialysis visiting stage and post-dialysis visiting stage every 12 to 24 weeks. The following data were recorded on standardized online electric case report forms (eCRFs). The primary endpoints include all-cause and cerebro-cardiovascular mortality. The secondary endpoints include non-fatal cerebro-cardiovascular events, annual hospitalization rate, quality of life, medical costs, and hemodialysis related complications.

Ethics and dissemination The study was approved on 31 October 2017 by the Ethics Committee of the First Affiliated Hospital of Dalian Medical University China (Registration No: YJ-KY-2017-119). We aim to present the final results of the ADIFE trial in peer-reviewed journals, Clinical Practice Guideline and at scientific meetings within 3 years after the start of the recruitment.

Trial registration number： ClinicalTrial.gov. NCT03385902; Pre-results.

Keywords End-Stage Renal Disease; Hemodialysis; Timing of Dialysis Initiation; Fuzzy mathematics.

Strengths and limitations of this study

► We established a novel and quantifiable equation, named DIFE, which contains nine laboratory and clinical parameters together that influence the timing of dialysis initiation by a retrospective cohort study, which we found a significant advantages of the DIFE for assessing the timing of dialysis initiation than estimate glomerular

filtration rate（eGFR）alone.

► This is the first prospective randomized controlled study to assess the timing for initiation of dialysis based on DIFE in patients with ESRD.

► The study will provide acceptability and feasibility data for optimal dialysis initiation based on DIFE avoiding early and late start dialysis in ESRD patients.

► limitations: All participants will be recruited from 28 hemodialysis centers in mainland china which may be associated with sample selection bias.

► limitations: there is no uniform dialyzer across all hemodialysis centers during dialysis treatment of participants.

Introduction

The growing prevalence and incidence rate of ESRD is a global challenge[1]. Hemodialysis is the main treatment for patients with ESRD, and its start time has a significant effect on the survival patients with ESRD[2-4]. Late and early start for dialysis can negatively affect the quality of life and survival prognosis of patients, and this sub-optimal timing results in economic burdens for families and society[5-7]. Therefore, the optimal time to commence dialysis can improve a patient's quality of life by relieving a patient's uremic symptoms, lowering the patient's risk of death, and by reducing medical care costs[4]. However, there is still no consensus on the optimal timing for ESRD patients to initiate dialysis, and it also remains uncertain whether the early or late initiation of dialysis was associated with better outcomes. Several observational studies found that earlier start of dialysis were associated with improved survival and better prognosis[5, 8, 9] .However，some cohort studies and a randomized controlled trial of the Initiating Dialysis Early and Late (IDEAL) study have shown that patients with early initiation of dialysis were associated with a poor survival and that late initiation of dialysis had a lower risk of mortality and improved survival[10-13]. These aforementioned findings are controversial mainly due to inefficient or outdated methods for assessing dialysis timing. All of the above studies used the creatinine-based estimate glomerular filtration rate (eGFR), a value whose specificity is affected by nutritional status and muscle mass, calculated by either the Modified Diet in Renal Disease equation or the Cockcroft-Gault equation[14, 15]. Studies showed

that some clinical factors such as old age, volume overload, malnutrition, diabetes, and heart failure strongly influenced the timing of dialysis initiation[5, 16-18]. Therefore, Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guideline for Hemodialysis Adequacy recommend that the decision to initiation maintenance dialysis should be based primarily on assessment of specific complications of kidney disease, including signs and symptoms of uremia, protein-energy wasting, metabolic abnormalities, and volume overload, rather than based on the eGFR alone[19, 20]. The deviation from an empirical decision to an assessment of varying clinical conditions inevitably leads to a lack of consensus due to the doctor's subjective judgements, which can lead to a sub-optimal decision of early or late initiation of dialysis.

Thus, the research team established a novel equation of timing of dialysis initiation based on a Fuzzy mathematical method (DIFE) derived from a previous multicenter retrospective cohort study with large-scale samples. The DIFE includes 9 parameters of sex, age, blood urea nitrogen, serum creatinine, hemoglobin, albumin, serum phosphorus, heart failure condition, and diabetes condition which effectively combines subjective clinical variables with objective biochemical markers for dialysis initiation decision making. The DIFE study showed that the 3 years dialysis mortality of patients in the optimal start group (DIFE between 30 to 35) was 9.9 % significantly lower than the late start group (DIFE less than 30) of 19.2%. Moreover, ROC curve analysis indicated that the area under ROC (AUROC) of prediction of 3 years death in hemodialysis initiation assessed by the DIFE was significantly higher than that by eGFR (0.73 versus 0.55, $p<0.01$). Therefore，the DIFE was more accurate and effective for assessing the timing of dialysis initiation than eGFR alone. Furthermore, the DIFE equation was convenient for popularization and application owing to transforming the subjective clinical factors into objective parameters, especially for non-nephrologist and doctors in primary hospitals. It may be the new standard in the assessment of the timing of dialysis replacing eGFR.

To further evaluate the predictive ability and clinical accuracy of DIFE, we designed a prospective multicenter randomized controlled trial from 28 hospitals located in different regions in China to assess clinical outcomes of ESRD patients, placed in

optimal or late start dialysis cohorts on the basis of DIFE. The aims of the trial to assess the effect of the optimal and late start dialysis, based on DIFE, using the 3 years mortality, hospitalization, morbidity, quality of life, and medical costs of hemodialysis patients. The ADIFE study will provide clinical evidence for the optimal time to start dialysis in ESRD patients based on DIFE.

Methods and analysis

Study design

The ADIFE study is a prospective, multicenter, randomized controlled, open-label trial in ESRD patients. which was divided into an "optimal start dailysis" group with DIFE value between 30 and 35 and a "late start dailysis" group with DIFE value less than 30 respectively. The study will be implemented in 28 dialysis centers, covering the seven administrative regions in China (North China, East China, South Central, Northeast, Southwest and Northwest). Each participating center has systemic follow-up for the participants with chronic kidney disease and can afford predialysis care including preparation of vascular access in patients approaching hemodialysis.

Participants will be followed up at baseline, pre-dialysis visiting stage every 12 weeks, and post-dialysis visiting stage every 12 or 24 weeks. The whole trial flow diagram is detailed in Figure 1. The protocol of ADIFE study was designed according to the SPIRIT reporting guidelines[21].

Participants

Inclusion criteria

Participants will enroll the study if they meet all the following requirements

a. Adults age between 18 to 75 years old;
b. Chronic kidney disease with an eGFR (calculated by the CKD-EPI equation[22]) less than 15mL/min/1.73m^2 and the DIFE between 30 and 35;
c. Expected to commence maintenance hemodialysis;
d. Agreeable to randomization.

Exclusion criteria

Participants will be excluded if meet the one of the following items

a. Acute kidney injury (AKI) or AKI on chronic kidney diseases (CKD);

b. With the primary disease of systemic lupus erythematosus（SLE）or systemic vasculitis;

c. Have received or planning to receive a kidney transplant or peritoneal dialysis;

d. Recently diagnosed cancer that was likely to impact on survival (except for cured cancer or remission for over 5 years, after radical resection of the basal cell carcinoma or squamous carcinoma of skin or carcinoma in-situ of any part of the body);

e. Hepatocirrhosis;

f. Positive test of Human Immunodeficiency Virus (HIV), the hepatitis B virus antigen (HBsAg) or anti-hepatitis C virus antibody (HCV Ab);

g. Acute infection disease within 1 month;

h. Bad habit which is difficult to withdrawal such as alcohol abuse;

i. Poor compliance;

j. Being pregnant, nursing or planing for pregnancy;

k. Life expectancy less than 1 year;

l. The investigator confirm that should not enroll in the study with any other cases.

Sample size considerations and Randomization

The sample size was calculated based on the results of DIFE study by retrospective cohort study, which showed the difference of the 3 years mortality rate between the optimal start dialysis group and late start dialysis group was 9.3%. As reported by the IDEAL study, the difference in the median time from randomization to the initiation of dialysis between the “early start” group and “late start” group was 5.6 months[10]. We assumed the time of dialysis initiation in the late start dialysis group would lag 6 months compared to the optimal start dialysis group. Therefore, the dialysis mortality rate of the late start dialysis group should be 2.5 years instead of 3 years. The power calculations using a a study-wide type I error rate (α) of 0.05, a type II error rate (β) of 0.2, and two-tailed statistical tests. The power analysis indicated that 225 participants would be required in each group. Allowing for an attrition rate of 10%, a total of 496 participants, or 248 in each group will be recruited.

After all 496 participants signed the informed consent form, the presence of the

inclusion criteria and the absence of the non-inclusion criteria was verified. Randomization will be carried out centrally using the internet-based randomization service (Randomization and Trial Supply Management system). Patients are stratified by center, Enrolled patients are randomly assigned 1:1 to optimal start dailysis group or late start dailysis group. Randomization allocation will be sent by automated email, to the non-blind researcher performing the randomization using their unique user name and password.

Treatment

All participants receive regular treatment as usual, which include regular dietary advice, anemia and Chronic Kidney Disease-Mineral and Bone Disorder management, blood pressure, and volume control as recommended by the KDIGO guideline and Chinese Hemodialysis Adequacy guidelines[19, 23-26]. Different types of vascular access including temporary venous catheters, arteriovenous fistula, and artificial blood vessel are permitted to be used in all participants. The use of such catheters is based only on clinical requirements. Each participating center has been advised to consider early access creation in each participant to avoid delay in the subsequent hemodialysis treatment.

All participants undergoing hemodialysis treatment with capacity control dialysis machine, bicarbonate dialysate, blood flow volume with 200 ~ 300ml/min, disposable high-flux or low-flux dialyzer with membrane area 1.3 ~ 1.6m^2, dialysis dose is 4 hours per treatment with 2 or 3 times in one week; and the recommended spKt/V is more than 1.2[19, 26, 27]. However, despite the existence of dialysis management guidelines in China, there is still potential for treatment variation between the participating centers.

Intervention

Participants allocated to the 'optimal start dialysis' group will commence dialysis with the DIFE values between 30 and 35. Participants allocated to the "late start dialysis" group were monitored based on the changes in DIFE values in the pre-dialysis visiting stage every 12 weeks until their DIFE values were less than 30, and then commenced dialysis. Participants allocated to the "late start dialysis" group are able to commence

dialysis earlier based on the recommendation of their caring physician although the DIFE no less than 30, for instance, Participants appearing obvious uremia symptoms, volume overload, hyperkalaemia and so on, which the reasons for the early initiation of dialysis to be recorded, this will allow for a subsequent analysis of actual DIFE at the dialysis start time.

Outcome measurement

All enrolled participants will be followed up until death or until 144 weeks after the last patient is randomized. Participants with "late start dialysis" group were assessed every 12 weeks in the pre-dialysis visiting stage. During the period of post-dialysis visiting stage, data will be collected every 12 weeks in the first year of follow-up and every 24 weeks in the next two years of follow-up, The detailed follow-up items in different visiting stage showed in table 1.

Comprehensive demographic data (age, gender, race, height, weight, education, employment, etiology of ESRD, medical history, presence of comorbid conditions, collected on all participants at baseline. Virology examination (Hepatitis B Virus antigen, Hepatitis C virus antibody, Human immunodeficiency virus antibody, syphilis antibody), urine human chorionic gonadotropin (HCG) were tested in screening stage, Vital signs, which include temperature (T), heart rate (HR), respiratory rate (RR), non-invasive blood presure (BP) were monitored each follow-up. Biochemical indexes including blood cell count (Red Blood Cells, White Blood Cells, Platelets), hemoglobin (Hb), blood urea nitrogen (BUN), serum creatinine (Scr), eGFR, electrolytes (serum sodium, serum potassium, serum chloride, serum calcium, serum phosphate), alanine transaminase (ALT), glutamic-oxalacetic transaminease (AST), total bilirubin (T-BIL), blood glucose, serum lipid, serum ferrium(SF), parathyroid hormone (PTH), and ferritin were tested every 12-24 weeks in each participating center. Inflammatory biomarkers including high-sensitivity C-reactive protein (hs-CRP), IL-6, IL-10, TNF-α and β_2-microglobulin（β_2-MG）will be collected and tested every 24 weeks by central lab in the Kidney Disease Research Institute of Dalian Medical University. Nutritional status was assessed using Subjective Global Assessment (SGA)[28] and serum albumin level

every 24 weeks. Quality of life will be measured using the well-validated Kidney Disease Quality of Life Short Form™ (KDQOL-SF™)[29, 30] every 48 weeks; and cognitive function will be assessed using the Montreal Cognitive Assessment (MoCA)[31] every 24 weeks. Concomitant medications including calcium channel blockers (CCB), statins, angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), and erythropoiesis stimulating agents (ESAs) are also being collected at baseline and follow-up period. Medical costs will be recorded in pre-dialysis visiting stage and post-dialysis visiting stage by both the questionnaire and medical insurance records of the participants, including dialysis related costs, hospitalization related costs, and outpatient costs of comorbidities treatment.

The all following data will be recorded on standardized online electric case report forms (eCRFs) based on electronic data acquisition system. All adverse events （AE） will be recorded on the eCRFs on specific pages reserved for this purpose. Serious adverse events（SAE）are defined as death, life-threatening, hospitalization (or prolongation of initial hospitalization), cause disability or cause permanent damage, a congenital anomaly, or birth defect. Completed eCRFs entered into a secured central database for independent quality control and centralized analysis.

Table 1 The Follow-up items in different visiting stage of ADIFE study

Follow-up items	Screening stage	Pre-dialysis visiting stage	Post-dialysis visiting stage
			V0~V8（0~144w）
Signed informed consent form	√	-	-
Inclusion and exclusion criteria	√	-	-
Demographic data	√	-	-
Vital signs, physical examination	√	√	√（V0~V8）
Urine HCG	√	-	-
Virology examination	√	-	-
Blood routine test	√	√	√（V0~V8）
BUN, Scr, eGFR, Alb, Electrolytes,	√	√	√（V0~V8）
ALT, AST, T-BIL, Blood glucose,	-	-	√（V0、V4、V6、V8）

Serum lipid, serum Ferrium			
PTH, Ferritin	-	-	√（V0、V2、V4~V8）
Hs-CRP、IL-6、IL-10、TNF-α、β_2-MG	-	-	√（V0、V2、V4~V8）
KDQoL-SF	-	-	√（V0、V4、V6、V8）
MoCA	-	-	√（V0、V2、V4~V8）
SGA	-	-	√（V0、V2、V4~V8）
Vascular access	-	-	√（V0~V8）
Medical costs	-	√	√（V0~V8）
Complications related to dialysis	-	-	√（V0~V8）
AE、SAE	-	√	√（V0~V8）
Concomitant medications	-	√	√（V0~V8）

Note: "√" represent selected follow-up items; "-" represent not-selected follow-up items.

Endpoint measurements

The primary endpoints measure is all-cause mortality and cerebro-cardiovascular mortality within 3 years following randomization to "optimal start dialysis" or "late start dialysis" groups. Cerebro-cardiovascular mortality includes the deaths caused by myocardial infarction, stroke, heart failure, or arrhythmia. Secondary endpoints include cerebro-cardiovascular events (nonfatal myocardial infarction, nonfatal stroke, transient ischemic attack, new-onset angina, acute heart failure or severe arrhythmia which should to be hospitalized), infectious complications, hemodialysis complications (including changes of vascular access, vascular access related infection, fluid and electrolyte disorders, and cognitive dysfunction), annual hospitalization (proportion of participants admitted to hospital every year), quality of life, nutrition assessment，cognitive dysfunction，and medical costs.

Statistical analysis

Qualitative variables will be described as number and percentage, and quantitative variables as number, mean, and standard deviation. Quantitative variables with skewed distributions will be presented as median and interquartile range (25th percentile to 75th percentile). Survival analysis will be on an intention-to-treat basis ("optimal start dialysis" vs "late start dialysis" based on the randomization allocation), Data will be censored for participants that do not reach the endpoint. The

characteristics of the two groups will be compared using the usual univariate tests (chi-squared or Fisher's exact test for categorical variables, and Student's unpaired t-test or the Wilcoxon rank-sum test for quantitative variables, as appropriate). The primary outcome will be analyzed by an unadjusted COX proportional hazards model, with secondary analysis by the Kaplan-Meier survival analysis. The comparison of the secondary outcomes will be the same as the baseline characteristics tests. SAll analyses will be performed using SAS Version 9.2 (SAS Institute Inc, Cary, NC, USA) by the team of statisticians at the Fuwai Hospital, China. The significance level is set at 0.05 for all final analyses.

Ethics and dissemination

Ethics

The study protocol was approved by the ethics committees of the First Affiliated Hospital of Dalian Medical University (YJ-KY-2017-119), and all participating centers will obtain additional ethics approval in accordance with local practice.

Informed consent and withdrawal from the study

Each participant or authorised surrogates will sign an informed consent form. The process of informed consent will be in accordance with the Declaration of Helsinki. Participants were fully informed about the ADIFE study by the investigators; and were able to discuss the trial process with their nephrologists and contact the investigator directly to request further information. participants and authorised surrogates will received the related materials of informed consent. Participants were informed of their right to withdraw at any time without their care being affected in any way.

Dissemination plan

Survey data will be exported directly from eCRF as a text file and imported in electronic form for scoring and analysis using statistics software. A detailed database will track participants' progress through the trial including the scheduling of assessments and reminders to complete assessments. Detailed strategies, including phone or text message reminders will be used to remind participants about upcoming assessments. All members of the research team and other associated personnel will

have access to the final trial dataset in both identified and re-identifiable forms.

Print data will be stored in locked filing cabinets accessible only to the research team. Electronic data will bestored on password-protected computers or servers only accessible to the research team. All paper and electronic records will be retained and disposed of in accordance with the requirements of the Criterions for the Quality Control of Clinical Trial from Drugs China Food and Drug Administration （CFDA）.

Results from the outcome measures will not be presented in a way that adversely affects the confidentiality of participants. The description of participants will not allow identification of individual participants, and individual results and individual names will not be revealed. Final reports and publications will only consist of aggregated results. At the completion of the study, participants will receive a plain Chinese summary of study results. Scientific reports of the main outcomes, secondary outcomes and process evaluation will be submitted to an international peer-reviewed journals. Results will also be presented at national and international conferences relevant to the subject fields.

Data management

All information of participants will be recorded on standardized online electric case report forms (eCRFs) which will be anonymized and saved on password-protected computers. The data monitoring committee (DMC) is independent from the sponsor and competing interests, will meet twice yearly to review the efficacy and safety data.

Oversight committees

A Trial Steering Committee has been set-up and will include an independent chairman, 28 independent members and the study's investigators.

Safety monitoring

AE will be closely monitored. These are events that are likely to affect to a significant degree the safety or physical or mental integrity of the participants in the trial. SAE must be reported to the sponsor (First Affiliated Hospital of Dalian Medical University, China) and the State Food and Drug Administration promptly by fax or telephone by investigators, followed by a written report within 24 hours, The sponsor

will be notified immediately of any case where the above definition applies during the trial.

Discussion

The timing of dialysis initiation is a risk factor affecting the prognosis of patients with ESRD. Optimal timing of dialysis initiation remains unclear. Some studies showed early start dialysis was associated with a lower risk of mortality[5] and others studies indicated either a survival advantage of late start dialysis[3, 11, 12, 32] or comparable mortality risk between early and late start dialysis[33, 34]. IDEAL study indicated that using eGFR as the primary guide for when to start dialysis likely should be abandoned in a patient with progressive advanced CKD[10].

The noval DIFE integrate subjective clinical variables of uremic signs and symptoms with objective biochemical markers beyond serum creatinine and eGFR for assessing timing of dialysis initiation in ESRD patients, which provide a individualized, effective and convenient tool for dialysis initiation decision making. The results of ADIFE study will provide solid evidence for evaluating the accuracy and efficacy of DIFE and maybe provide the potentail optimal timing of dialysis initiation with ESRD patients approaching the need for maintenance dialysis.

Author Contributors

All authors meet ICMJE criteria for authorship in that they have contributed substantially to the conceptual design or the processes of data collection, analysis or interpretation, the drafts and revisions of the study protocol and manuscript, granted approval of the final version of the study protocol and acknowledged their accountability with regard to the integrity and accuracy of this study protocol.

Research idea and study design: Hongli Lin, Xiangmei Chen and Xuefeng Sun.

Writing and reviewing of the protocol: Jilin chen, Ying Liu, Hongli Lin and Yang Wang.

Drafting of the manuscript: Jilin chen and Ying Liu will be responsible for administrative and managerial procedures related to all phases of the trial, which will be supervised by Hongli Lin.

Statistical analysis: Yang Wang, and Wei Li.

Trial status

Recruitment will commence using digital social media networks and print-based advertising nationwide in April 2018. Completion of recruitment is expected in December 2018. The study will be completed in December 2021.

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Conflicts of interests None declared.

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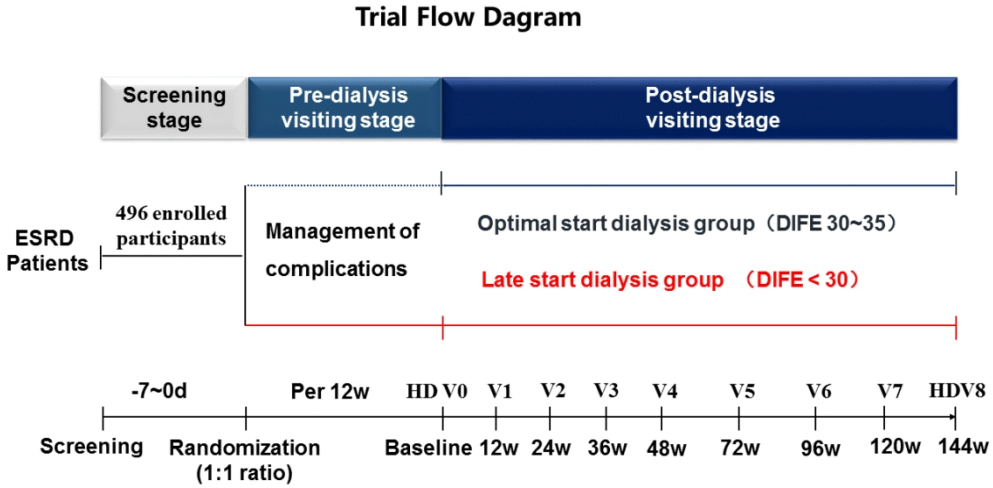

Trial Flow Diagram

451x254mm (72 x 72 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

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Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	4
Protocol version	#3	Date and version identifier	4
Funding	#4	Sources and types of financial, material, and other support	16
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1-3,15
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	16

sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	,16
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	14
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-6
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5-6
Objectives	#7	Specific objectives or hypotheses	6-7
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	7
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	9-10
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	9-10
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-11
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	15
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed	9

mechanism		envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12-13
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12-13
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12-13

Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	13
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	13
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	n/a
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	13
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Data access	#29	Statement of who will have access to the final trial dataset,	13

		and disclosure of contractual agreements that limit such access for investigators	
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	13
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

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Assessment of Dialysis Initiation by a Fuzzy mathematics Equation (ADIFE): a study protocol for a randomised controlled trial

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Primary Subject Heading:	Renal medicine
Secondary Subject Heading:	Evidence based practice
Keywords:	End-Stage Renal Disease, Hemodialysis, Timing of Dialysis Initiation, Fuzzy mathematics

Assessment of Dialysis Initiation by a Fuzzy mathematics Equation (ADIFE): a study protocol for a randomised controlled trial

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Abstract

Introduction Starting dialysis early and late results in a lower quality of life and a poor prognosis in hemodialysis patients. However, there remains no consensus on the optimal timing of dialysis initiation mainly due to the lack of suitable methods to assess variations in dialysis start times. We established a novel equation named DIFE (Dialysis Initiation based on Fuzzy-mathematics Equation) through a previous retrospective multicenter clinical cohort study in mainland China. The parameters of the DIFE include nine biochemical markers and clinical variables altogether influence dialysis initiation. To verify the external validity and clinical accuracy of DIFE, we designed the ADIFE (assessment of DIFE) study with a prospective, multicenter,

randomized controlled, open-label trial to assess the clinical outcomes between patients who initiate dialysis in an optimal start dialysis group and a late start dialysis group based on DIFE.

Methods and analysis A total of 496 enrolled end-stage renal disease (ESRD) subjects will be randomised 1:1 to the optimal start group with DIFE value between 30 and 35 or late start dialysis group with DIFE value less than 30 using the Randomization and Trial Supply Management (RTSM) system. Participants will be assessed with signs and symptoms change, dialysis mode and parameters, biochemical and inflammatory markers, Subjective Global Assessment (SGA), Kidney Disease Quality of Life Short Form (KDQOL-SF^{TM}), Cognitive Assessment (MoCA), Medical costs, adverse events, and concomitant medication at baseline, pre-dialysis visiting stage and post-dialysis visiting stage every 12 to 24 weeks. The following data were recorded on standardized online electric case report forms (eCRFs). The primary endpoints is all-cause mortality. The secondary endpoints include non-fatal cerebro-cardiovascular events, annual hospitalization rate, quality of life, medical costs, and hemodialysis related complications.

Ethics and dissemination Ethical approval was obtained from the Ethics Committee of the First Affiliated Hospital of Dalian Medical University China (Registration No: YJ-KY-2017-119).

The final results of the ADIFE trial will be presented to the study sponsor, clinical researchers and patient and public involvement. Findings will be disseminated through peer-reviewed journals, Clinical Practice Guideline and at scientific meetings.

Trial registration number： ClinicalTrial.gov. NCT03385902; Pre-results.

Keywords End-Stage Renal Disease; Hemodialysis; Timing of Dialysis Initiation; Fuzzy mathematics.

Strengths and limitations of this study

► We established a novel and quantifiable equation, named DIFE, which contains nine laboratory and clinical parameters together that influence the timing of dialysis initiation by a retrospective cohort study, which we found a significant advantages of the DIFE for assessing the timing of dialysis initiation than estimate glomerular

filtration rate（eGFR）alone.

► This is the first prospective randomized controlled study to assess the timing for initiation of dialysis based on DIFE in patients with ESRD.

► The study will provide acceptability and feasibility data for optimal dialysis initiation based on DIFE avoiding early and late start dialysis in ESRD patients.

► limitations: All participants will be recruited from 28 hemodialysis centers in mainland china which may be associated with sample selection bias.

► limitations: There is no uniform dialyzer across all hemodialysis centers during dialysis treatment of participants.

Introduction

The growing prevalence and incidence rate of ESRD is a global challenge[1]. Hemodialysis is the main treatment for patients with ESRD, and its start time has a significant effect on the survival patients with ESRD[2-4]. Late and early start for dialysis can negatively affect the quality of life and survival prognosis of patients, and this sub-optimal timing of dialysis results in economic burdens for families and society[5-7]. Therefore, the optimal time to commence dialysis can improve a patient's quality of life by relieving a patient's uremic symptoms, lowering the patient's risk of death, and by reducing medical care costs[4]. However, there is still no consensus on the optimal timing for ESRD patients to initiate dialysis, and it also remains uncertain what is exactly optimal timing of dialysis was associated with better outcomes. Several observational studies found that earlier start of dialysis were associated with improved survival and better prognosis[5, 8, 9] .However，some cohort studies and a randomized controlled trial of the Initiating Dialysis Early and Late (IDEAL) study have shown that patients with early initiation of dialysis were associated with a poor survival and that late initiation of dialysis had a lower risk of mortality and improved survival[10-13]. These aforementioned findings are controversial mainly due to inefficient or outdated methods for assessing dialysis timing. All of the above studies used the creatinine-based estimate glomerular filtration rate (eGFR), a value whose specificity is affected by nutritional status and muscle mass, calculated by either the Modified Diet in Renal Disease equation or the

Cockcroft-Gault equation[14, 15]. Studies showed that some clinical factors such as old age, volume overload, malnutrition, diabetes, and heart failure strongly influenced the timing of dialysis initiation[5, 16-18]. Therefore, Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guideline for Hemodialysis Adequacy recommend that the decision to initiation maintenance dialysis should be based primarily on assessment of specific complications of kidney disease, including signs and symptoms of uremia, protein-energy wasting, metabolic abnormalities, and volume overload, rather than based on the eGFR alone[19, 20]. The deviation from an empirical decision to an assessment of varying clinical conditions inevitably leads to a lack of consensus due to the doctor's subjective judgements, which can lead to a sub-optimal decision of early or late initiation of dialysis.

Thus, the research team established a novel equation of timing of dialysis initiation based on a Fuzzy mathematical method (DIFE) derived from a previous multicenter retrospective cohort study with large-scale samples. The DIFE includes 9 parameters of sex, age, blood urea nitrogen, serum creatinine, hemoglobin, albumin, serum phosphorus, heart failure condition, and diabetes condition which effectively combines subjective clinical variables with objective biochemical markers for dialysis initiation decision making. The DIFE study showed that the 3 years dialysis mortality of patients in the optimal start group (DIFE between 30 to 35) was 8.38% significantly lower than the late start group (DIFE less than 30) of 19.4%. Moreover, ROC curve analysis indicated that the area under curve (AUC) of prediction of 3 years death in dialysis initiation assessed by the DIFE was significantly higher than that by eGFR (0.73 versus 0.55, P <0.01). Therefore，the DIFE was more accurate and effective for assessing the timing of he modialysis initiation than eGFR alone. Furthermore, the DIFE equation was convenient for popularization and application owing to transforming the subjective clinical factors into objective parameters, especially for non-nephrologist and doctors in primary hospitals. It may be the new standard in the assessment of the timing of dialysis replacing eGFR. To further evaluate the predictive ability and clinical accuracy of DIFE, we designed a prospective multicenter randomized controlled trial

from 28 hospitals located in different regions in China to assess clinical outcomes of ESRD patients, placed in optimal or late start dialysis cohorts on the basis of DIFE. The aims of the trial to assess the effect of the optimal and late start dialysis, based on DIFE, using the 3 years mortality, hospitalization, morbidity, quality of life, and medical costs of hemodialysis patients. The ADIFE study will provide clinical evidence for the optimal time to start dialysis in ESRD patients based on DIFE.

Methods and analysis

Study design

The ADIFE study is a prospective, multicenter, randomized controlled, open-label trial in ESRD patients. which was divided into an "optimal start dialysis" group with DIFE value between 30 and 35 and a "late start dialysis" group with DIFE value less than 30 respectively. The study will be implemented in 28 dialysis centers, covering the seven administrative regions in China (North China, East China, South Central, Northeast, Southwest and Northwest). Each participating center has systemic follow-up for the participants with chronic kidney disease and can afford predialysis care including preparation of vascular access in patients approaching hemodialysis.

Participants will be followed up at baseline, pre-dialysis visiting stage every 12 weeks, and post-dialysis visiting stage every 12 or 24 weeks. The whole trial flow diagram is detailed in Figure 1. The protocol of ADIFE study was designed according to the SPIRIT reporting guidelines[21].

Participants

Inclusion criteria

Participants will enroll the study if they meet all the following requirements

a. Adults age between 18 to 75 years old;
b. Chronic kidney disease with an eGFR (calculated by the CKD-EPI equation[22]) less than 15mL/min/1.73m^2 and the DIFE between 30 and 35;
c. Expected to commence maintenance hemodialysis;
d. Agreeable to randomization.

Exclusion criteria

Participants will be excluded if meet the one of the following items

a. Acute kidney injury (AKI) or AKI on chronic kidney diseases (CKD);
b. With the primary disease of systemic lupus erythematosus（SLE）or systemic vasculitis;
c. Have received or planning to receive a kidney transplantation or peritoneal dialysis;
d. Recently diagnosed cancer that was likely to impact on survival (except for cured cancer or remission for over 5 years, after radical resection of the basal cell carcinoma or squamous carcinoma of skin or carcinoma in-situ of any part of the body);
e. Hepatocirrhosis;
f. Positive test of Human Immunodeficiency Virus (HIV), the hepatitis B virus antigen (HBsAg) or anti-hepatitis C virus antibody (HCV Ab);
g. Acute infection disease within 1 month;
h. Bad habit which is difficult to withdrawal such as alcohol abuse;
i. Poor compliance;
j. Being pregnant, nursing or planing for pregnancy;
k. Life expectancy less than 1 year;
l. The investigator confirm that should not enroll in the study with any other cases.

Sample size

The sample size was calculated mainly based on the all-cause mortality results of DIFE study by retrospective cohort study, which showed that the 3 years mortality of the optimal start group was 8.38% and that of the late start group was 19.4%. The difference between the two groups was optimistic. However, hemodialysis centers of the DIFE study are all the best hemodialysis centers in China and the mortality of hemodialysis patients in these centers are lower than the national average level. According to the Chinese National Renal Data System（CNRDS）report in 2016, the 3 years mortality of patients after hemodialysis was 30.6%, and based on the experience of the IDEAL study[23]. We assumed 3 years mortality in the optimal start group and late start group to be 10% and 20%. Therefore, we estimated a sample size of 198 per group (assuming I error rate (α) of 0.05, a type II error rate (β) of 0.2, two-sided test,

with $P<0.05$ considered statistically significant). Assuming that 20% of participants would withdraw or drop out, the target sample size was 496 participants, or 248 participants in each group will be recruited.

Randomization and allocation

Independent biostatisticians with no relationship to the data management and data statistical analysis team will use the SAS 9.2 software (version 9.1.3; SAS Institute, Inc., Cary, NC, USA) stratified by site to generate random numbers according to the block randomization method.The investigators will allocate the random numbers to eligible participants assigned 1:1 to optimal start dialysis group or late start dialysis group according to the enrollment sequence. Randomization allocation and random number will be sent by automated email, to the non-blind investigators performing the randomization using their unique user name and password on the internet-based randomization service of Randomization and Trial Supply Management system.

Patient and Public Involvement

A patient and public involvement (PPI) reference group comprising dialysis patients, their partners, carers and representatives from Voluntary Sectors will be formed. The PPI reference group will meet quarterly throughout the duration of the program. Group members have been consulted at all stages of the work leading to this proposal, provided valuable insight and advice. The trial was designed in partnership with PPI to help maximizing patient benefits. Our PPI representatives have materially influenced decisions on the study population, promotion and recruitment, they will also continue to contribute throughout this pilot study in terms of reviewing documentation for ethics approval, reading reports and contributing to dissemination activities. We will also present the final results of the ADIFE trial to PPI.

Treatment

All participants receive regular treatment as usual, which include regular dietary advice, anemia and Chronic Kidney Disease-Mineral and Bone Disorder management, blood pressure, and volume control as recommended by the KDIGO guideline and Chinese Hemodialysis Adequacy guidelines[19, 24-27]. Different types of vascular access including temporary venous catheters, arteriovenous fistula, and artificial blood vessel

are permitted to be used in all participants. The use of such catheters is based only on clinical requirements. Each participating center has been advised to consider early access creation in each participant to avoid delay in the subsequent hemodialysis treatment.

All participants undergoing hemodialysis treatment with capacity control dialysis machine, bicarbonate dialysate, blood flow volume with 200 ~ 300ml/min, disposable high-flux or low-flux dialyzer with membrane area 1.3 ~ 1.6m^2, dialysis dose is 4 hours per treatment with 2 or 3 times in one week; and the recommended spKt/V is more than 1.2[19, 27, 28]. However, despite the existence of dialysis management guidelines in China, there is still potential for treatment variation between the participating centers.

Intervention

Participants allocated to the 'optimal start dialysis' group will commence dialysis with the DIFE values between 30 and 35. Participants allocated to the "late start dialysis" group were monitored based on the changes in DIFE values in the pre-dialysis visiting stage every 12 weeks until their DIFE values were less than 30, and then commenced dialysis. Participants allocated to the "late start dialysis" group are able to commence dialysis earlier based on the recommendation of their caring physician although the DIFE no less than 30, for instance, Participants appearing obvious uremia symptoms, volume overload, hyperkalemia and so on, which the reasons for the early initiation of dialysis to be recorded, this will allow for a subsequent analysis of actual DIFE at the dialysis start time.

Outcome measurement

All enrolled participants will be followed up until death or until 144 weeks after the last patient is randomized. Participants with "late start dialysis" group were assessed every 12 weeks in the pre-dialysis visiting stage. During the period of post-dialysis visiting stage, data will be collected every 12 weeks in the first year of follow-up and every 24 weeks in the next two years of follow-up, The detailed follow-up items in different visiting stage showed in table 1.

Comprehensive demographic data (age, gender, ethnicity, height, weight,

education, employment, etiology of ESRD, medical history, presence of comorbid conditions, collected on all participants at baseline. Virology examination (Hepatitis B virus antigen, hepatitis C virus antibody, human immunodeficiency virus antibody, syphilis antibody), urine human chorionic gonadotropin (HCG) were tested in screening stage, vital signs, which include temperature (T), heart rate (HR), respiratory rate (RR), non-invasive blood presure (BP) were monitored each follow-up. Biochemical indexes including blood cell count (Red Blood Cells, White Blood Cells, Platelets), hemoglobin (Hb), blood urea nitrogen (BUN), serum creatinine (Scr), eGFR, electrolytes (serum sodium, serum potassium, serum chloride, serum calcium, serum phosphate), alanine transaminase (ALT), glutamic-oxalacetic transaminease (AST), total bilirubin (T-BIL), blood glucose, serum lipid, serum ferrium(SF), parathyroid hormone (PTH), and ferritin were tested every 12-24 weeks in each participating center. Inflammatory biomarkers including high-sensitivity C-reactive protein (hs-CRP), IL-6, IL-10, tumor necrosis factor-α （TNF-α） and β_2-microglobulin（β_2-MG）will be collected and tested every 24 weeks by central lab in the Kidney Disease Research Institute of Dalian Medical University. Nutritional status was assessed using Subjective Global Assessment (SGA)[29] and serum albumin level every 24 weeks. Quality of life will be measured using the well-validated Kidney Disease Quality of Life Short Form™ (KDQOL-SF™)[30, 31] every 48 weeks; and cognitive function will be assessed using the Montreal Cognitive Assessment (MoCA)[32] every 24 weeks. Concomitant medications including calcium channel blockers (CCB), statins, angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), and erythropoiesis stimulating agents (ESAs) are also being collected at baseline and follow-up period. Medical costs will be recorded in pre-dialysis visiting stage and post-dialysis visiting stage by both the questionnaire and medical insurance records of the participants, including dialysis related costs, hospitalization related costs, and outpatient costs of comorbidities treatment.

The all following data will be recorded on standardized online electric case report forms (eCRFs) based on electronic data acquisition system. All adverse events

（AE）will be recorded on the eCRFs on specific pages reserved for this purpose. Serious adverse events（SAE）are defined as death, life-threatening, hospitalization (or prolongation of initial hospitalization), cause disability or cause permanent damage, a congenital anomaly, or birth defect. Completed eCRFs entered into a secured central database for independent quality control and centralized analysis.

Table 1 The Follow-up items in different visiting stage of ADIFE study

Follow-up items	Screening stage	Pre-dialysis visiting stage	Post-dialysis visiting stage
			V0~V8（0~144w）
Signed informed consent form	√	-	-
Inclusion and exclusion criteria	√	-	-
Demographic data	√	-	-
Vital signs, physical examination	√	√	√（V0~V8）
Urine HCG	√	-	-
Virology examination	√	-	-
Blood routine test	√	√	√（V0~V8）
BUN, Scr, eGFR, Alb, Electrolytes,	√	√	√（V0~V8）
ALT, AST, T-BIL, Blood glucose, Serum lipid, serum Ferrium	-	-	√（V0、V4、V6、V8）
PTH, Ferritin	-	-	√（V0、V2、V4~V8）
Hs-CRP、IL-6、IL-10、TNF-α、β_2-MG	-	-	√（V0、V2、V4~V8）
KDQoL-SF	-	-	√（V0、V4、V6、V8）
MoCA	-	-	√（V0、V2、V4~V8）
SGA	-	-	√（V0、V2、V4~V8）
Vascular access	-	-	√（V0~V8）
Medical costs	-	√	√（V0~V8）
Complications related to dialysis	-	-	√（V0~V8）
AE、SAE	-	√	√（V0~V8）
Concomitant medications	-	√	√（V0~V8）

Note: "√" represent selected follow-up items; "-" represent not-selected follow-up items.HCG, human chorionic gonadotropin; BUN, blood urea nitrogen; Scr,serum creatinine; eGFR, estimate glomerular filtration rate; ALB, albumin; ALT, alanine transaminase; AST, glutamic-oxalacetic transaminease; T-BIL, total bilirubin; PTH, parathyroid hormone; hs-CRP,

high sensitive C-reactive protein; TNF-α, tumor necrosis factor-α; β_2-MG, β_2-microglobulin; KDQOL-SF, Kidney Disease Quality of Life Short Form; MoCA, Montreal Cognitive Assessment; SGA, subjective global assessment; AE, adverse events; SAE, serious adverse events.

Endpoint measurements

The primary endpoints is all-cause mortality within 3 years following randomization to "optimal start dialysis" or "late start dialysis" groups. Secondary endpoints include cerebro-cardiovascular events (nonfatal myocardial infarction, nonfatal stroke, transient ischemic attack, new-onset angina, acute heart failure or severe arrhythmia which should to be hospitalized), infectious complications, hemodialysis complications (including changes of vascular access, vascular access related infection, fluid and electrolyte disorders, and cognitive dysfunction), annual hospitalization (proportion of participants admitted to hospital every year), quality of life, nutrition assessment，cognitive dysfunction and medical costs.

Statistical analysis

For all baseline and outcome variables, the number of available measurements and the number of missing values will be given. All analyses will be conducted according to the intention-to-treat principle, as recommended in the Consolidated Standards of Reporting Trials (CONSORT) statement. That is, all randomised patients will be analysed in the groups to which they were originally allocated. Qualitative variables will be described as number and percentage, and quantitative variables as number, mean, and standard deviation. Quantitative variables with skewed distributions will be presented as median and interquartile range (25th percentile to 75th percentile).

The characteristics of the two groups will be compared using the usual univariate tests (chi-squared or Fisher's exact test for categorical variables, and Student's unpaired t-test or the Wilcoxon rank-sum test for quantitative variables, as appropriate). We used a time-to-event analysis to compare the proportions of patients with primary and secondary outcomes in the two groups. The primary outcome of the all-cause mortality in 3 years will be compared between optimal start and late start groups using the Cochran-Mantel-Haenszel procedure, adjusting for center. In sensitivity analyses

of all-cause mortality, univariate and multivariate COX proportional hazard models with inverse probability weighting (IPW) will be performed to adjust for age, diabetes, cardiovascular diseases, cause of ESRD. All analyses will be performed using SAS Version 9.2 (SAS Institute Inc, Cary, NC, USA) by the team of statisticians at the Fuwai Hospital, China. All reported *P* values are two-sided and *P* values less than 0.05 will be considered to be significant.

Ethics and dissemination

Ethics

Ethical approval was obtained from the ethics committees of the First Affiliated Hospital of Dalian Medical University (Registration No:YJ-KY-2017-119), and all participating centers will also obtain additional ethics approval in accordance with local practice.

Informed consent and withdrawal from the study

Each participant or authorised surrogates will sign an informed consent form. The process of informed consent will be in accordance with the Declaration of Helsinki. Participants were fully informed about the ADIFE study by the investigators, and were able to discuss the trial process with their nephrologists and contact the investigator directly to request further information. Participants and authorised surrogates will received the related materials of informed consent. Participants were informed of their right to withdraw from the study either at their own request or at the discretion of the investigator at any time without their care being affected in any way.

Dissemination plan

Survey data will be exported directly from eCRF as a text file and imported in electronic form for scoring and analysis using statistics software. A detailed database will track participants' progress through the trial including the scheduling of assessments and reminders to complete assessments. Detailed strategies, including phone or text message reminders will be used to remind participants about upcoming assessments. All members of the research team and other associated personnel will have access to the final trial dataset in both identified and re-identifiable forms.

Print data will be stored in locked filing cabinets accessible only to the research

team. Electronic data will bestored on password-protected computers or servers only accessible to the research team. All paper and electronic records will be retained and disposed of in accordance with the requirements of the Criterions for the Quality Control of Clinical Trial from Drugs China Food and Drug Administration （CFDA）.

Results from the outcome measures will not be presented in a way that adversely affects the confidentiality of participants. The description of participants will not allow identification of individual participants, and individual results and individual names will not be revealed. Final reports and publications will only consist of aggregated results. At the completion of the study, participants will receive a plain chinese summary of study results. Scientific reports of the main outcomes, secondary outcomes and process evaluation will be submitted to an international peer-reviewed journals. Results will also be presented at national and international conferences relevant to the subject fields.

Data management

All information of participants will be recorded on standardized online electric case report forms (eCRFs) which will be anonymized and saved on password-protected computers. The data monitoring committee (DMC) is independent from the sponsor and competing interests, will meet twice yearly to review the efficacy and safety data.

Oversight committees

A Trial Steering Committee has been set-up and will include an independent chairman, 28 independent members and the study's investigators.

Safety monitoring

AE will be closely monitored. These are events that are likely to affect to a significant degree the safety or physical or mental integrity of the participants in the trial. SAE must be reported to the sponsor (First Affiliated Hospital of Dalian Medical University, China) and the State Food and Drug Administration promptly by fax or telephone by investigators, followed by a written report within 24 hours, The sponsor will be notified immediately of any case where the above definition applies during the trial.

Discussion

The timing of dialysis initiation is a risk factor affecting the prognosis of patients with ESRD. Optimal timing of dialysis initiation remains unclear. Some studies showed early start dialysis was associated with a lower risk of mortality[5] and others studies indicated either a survival advantage of late start dialysis[3, 11, 12, 33] or comparable mortality risk between early and late start dialysis[34, 35]. IDEAL study indicated that using eGFR as the primary guide for when to start dialysis likely should be abandoned in a patient with progressive advanced CKD[10].

The noval DIFE integrate subjective clinical variables of uremic signs and symptoms with objective biochemical markers beyond serum creatinine and eGFR for assessing timing of dialysis initiation in ESRD patients, which provide a individualized, effective and convenient tool for dialysis initiation decision making. The results of ADIFE study will provide solid evidence for evaluating the accuracy and efficacy of DIFE and maybe provide the potential optimal timing of dialysis initiation with ESRD patients approaching the need for maintenance dialysis. Some nephrologists and non-nephrologis with less trained who may not know how to interpret laboratory values and clinical signs a formula to calculate when to start dialysis can be very helpful to deliver safe care.

The DIFE formula were established through a previous retrospective multicenter cohort study with hemodialysis patients' data, the ADIFE study will further assess the clinical accuracy and availability of DIFE for guiding the timing of hemodialysis initiation, therefore, the ADIFE study excluded the Participants waiting peritoneal dialysis and transplantation, but we have already planned to assess the availability of DIFE for guiding the timing of dialysis with peritoneal dialysis patients through other clinical study.

Author contributors

All authors meet ICMJE criteria for authorship in that they have contributed substantially to the conceptual design or the processes of data collection, analysis or interpretation, the drafts and revisions of the study protocol and manuscript, granted approval of the final version of the study protocol and acknowledged their

accountability with regard to the integrity and accuracy of this study protocol.

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Trial status

Recruitment will commence using digital social media networks and print-based advertising nationwide in April 2018. Completion of recruitment is expected in December 2018. The study will be completed in December 2021.

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Conflicts of interests None declared.

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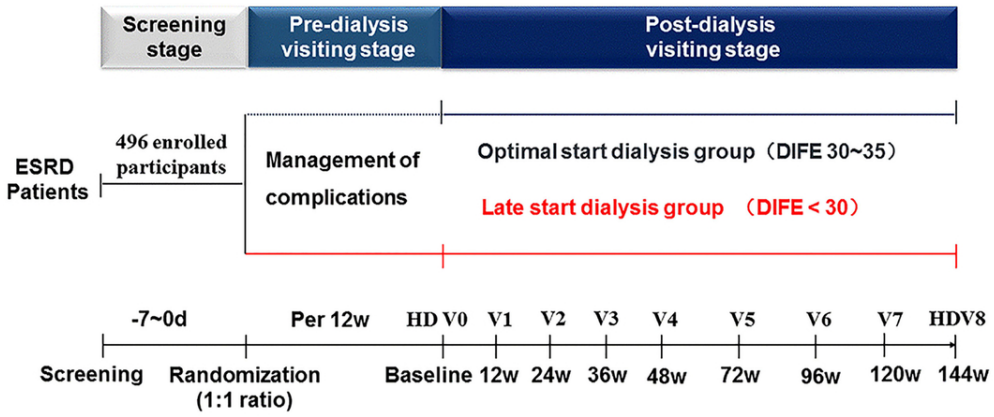
Figure legends

Figure 1 **Trial Flow Diagram of the ADIFE study.** The whole trial flow including the screening stage within seven days, pre-dialysis visiting stage and post-dialysis visiting stage of visit 0 ~ visit 8. Enrolled subjects will be randomised 1:1 to the optimal start dialysis group with DIFE value between 30 and 35 or late start dialysis group with DIFE value less than 30. Participants will be followed up at baseline（visit 0）, pre-dialysis visiting stage every 12 weeks, and post-dialysis visiting stage every 12 or 24 weeks. ESRD, End-Stage Renal Disease; DIFE, Dialysis Initiation based on Fuzzy-mathematics Equation.



Trial Flow Diagram of the ADIFE study

90x40mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	4
Protocol version	#3	Date and version identifier	n/a
Funding	#4	Sources and types of financial, material, and other support	17
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1-3,16
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	15

sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	17
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	15
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-7
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5-7
Objectives	#7	Specific objectives or hypotheses	6-7
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	7
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	9-10
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	9-12
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9-10
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-13
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	14
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed	9

mechanism		envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	15
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13

Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	15
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	15
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	14
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	n/a
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	14
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14-15
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Data access	#29	Statement of who will have access to the final trial dataset,	15

		and disclosure of contractual agreements that limit such access for investigators	
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	14
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

BMJ Open

Assessment of Dialysis Initiation by a Fuzzy mathematics Equation (ADIFE): a study protocol for a randomised controlled trial

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Secondary Subject Heading:	Evidence based practice
Keywords:	End-Stage Renal Disease, Hemodialysis, Timing of Dialysis Initiation, Fuzzy mathematics

Assessment of Dialysis Initiation by a Fuzzy mathematics Equation (ADIFE): a study protocol for a randomised controlled trial

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Abstract

Introduction Starting dialysis early or late both results in a low quality of life and a poor prognosis in hemodialysis patients. However, there remains no consensus on the optimal timing of dialysis initiation and this is mainly due to lack of suitable methods to assess variations in dialysis initiation time. We have established a novel equation named DIFE (Dialysis Initiation based on Fuzzy-mathematics Equation) through a retrospective multicenter clinical cohort study in China to find the most suitable timing of dialysis initiation. The predictors of the DIFE include nine biochemical markers and clinical variables altogether influence dialysis initiation. To verify the external validity and clinical accuracy of DIFE, we designed the ADIFE (assessment of DIFE) study by

a prospective, open-label, multicenter, randomized controlled trial to assess the clinical outcomes among patients who initiate dialysis in an optimal start dialysis group and a late start dialysis group based on DIFE.

Methods and analysis A total of 388 enrolled end-stage renal disease (ESRD) subjects will be randomised 1:1 to the optimal start group with DIFE value between 30 and 35 or late start dialysis group with DIFE value less than 30 using the Randomization and Trial Supply Management (RTSM) system. Participants will be assessed with signs and symptoms change, dialysis mode and parameters, biochemical and inflammatory markers, Subjective Global Assessment (SGA), Kidney Disease Quality of Life Short Form (KDQOL-SF^{TM}), Cognitive Assessment (MoCA), Medical costs, adverse events, and concomitant medication at baseline, pre-dialysis visiting stage and post-dialysis visiting stage every 12 to 24 weeks. The following data were recorded on standardized online electric case report forms (eCRFs). The primary endpoint is 3 years all-cause mortality. The secondary endpoints include non-fatal cerebro-cardiovascular events, annual hospitalization rate, quality of life, medical costs, and hemodialysis related complications.

Ethics and dissemination Ethical approval was obtained from the Ethics Committee of the First Affiliated Hospital of Dalian Medical University China (Registration No: YJ-KY-2017-119).

The final results of the ADIFE trial will be presented to the study sponsor, clinical researchers and patient and public involvement. Findings will be disseminated through peer-reviewed journals, Clinical Practice Guideline and at scientific meetings.

Trial registration number ClinicalTrial.gov. NCT03385902; Pre-results.

Keywords End-Stage Renal Disease; Hemodialysis; Timing of Dialysis Initiation; Fuzzy mathematics.

Strengths and limitations of this study

► We established a novel and quantifiable equation, named DIFE, which contains nine laboratory and clinical parameters together that influence the timing of dialysis initiation by a retrospective cohort study, which we found a significant advantages of

the DIFE for assessing the timing of dialysis initiation than estimate glomerular filtration rate（eGFR）alone.

► This is the first prospective randomized controlled study to assess the timing for initiation of dialysis based on DIFE in patients with ESRD.

► The study will provide acceptability and feasibility data for optimal dialysis initiation based on DIFE avoiding early and late start dialysis in ESRD patients.

► limitations: All participants will be recruited from 28 hemodialysis centers in china which may be associated with sample selection bias.

► limitations: There is no uniform dialyzer across all hemodialysis centers during dialysis treatment of participants.

Introduction

The growing prevalence and incidence rate of ESRD is a global challenge[1]. Hemodialysis is the main treatment for patients with ESRD, and its start time has a significant effect on the survival patients with ESRD[2-4]. Late and early start for dialysis can negatively affect the quality of life and survival prognosis of patients, and this sub-optimal timing of dialysis results in economic burdens for families and society[5-7]. Therefore, the optimal time to commence dialysis can improve a patient's quality of life by relieving a patient's uremic symptoms, lowering the patient's risk of death, and by reducing medical care costs[4]. However, there is still no consensus on the optimal timing for ESRD patients to initiate dialysis, and it also remains uncertain what is exactly optimal timing of dialysis was associated with better outcomes. Several observational studies found that earlier start of dialysis were associated with improved survival and better prognosis[5, 8, 9] .However， some cohort studies and a randomized controlled trial of the Initiating Dialysis Early and Late (IDEAL) study have shown that patients with early initiation of dialysis were associated with a poor survival and that late initiation of dialysis had a lower risk of mortality and improved survival[10-13]. These aforementioned findings are controversial mainly due to inefficient or outdated methods for assessing dialysis timing. All of the above studies used the creatinine-based estimate glomerular filtration rate (eGFR), a value whose specificity is affected by nutritional status and muscle mass, calculated by either the Modified Diet in Renal

Disease equation or the Cockcroft-Gault equation[14, 15]. Studies showed that some clinical factors such as old age, volume overload, malnutrition, diabetes, and heart failure strongly influenced the timing of dialysis initiation[5, 16-18]. Therefore, Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guideline for Hemodialysis Adequacy recommend that the decision to initiation maintenance dialysis should be based primarily on assessment of specific complications of kidney disease, including signs and symptoms of uremia, protein-energy wasting, metabolic abnormalities, and volume overload, rather than based on the eGFR alone[19, 20]. The deviation from an empirical decision to an assessment of varying clinical conditions inevitably leads to a lack of consensus due to the doctor's subjective judgements, which can lead to a sub-optimal decision of early or late initiation of dialysis.

Thus, the research team established a novel equation of timing of dialysis initiation based on a Fuzzy mathematical method (DIFE) derived from a previous multicenter retrospective cohort study with large-scale samples. The DIFE includes 9 parameters of sex, age, blood urea nitrogen, serum creatinine, hemoglobin, albumin, serum phosphorus, heart failure condition, and diabetes condition which effectively combines subjective clinical variables with objective biochemical markers for dialysis initiation decision making. The DIFE study showed that the 3 years dialysis mortality of patients in the optimal start group (DIFE between 30 to 35) was 8.38% significantly lower than the late start group (DIFE less than 30) of 19.4%. Moreover, ROC curve analysis indicated that the area under curve (AUC) of prediction of 3 years death in dialysis initiation assessed by the DIFE was significantly higher than that by eGFR (0.73 versus 0.55, P <0.01). Therefore，the DIFE was more accurate and effective for assessing the timing of he modialysis initiation than eGFR alone. Furthermore, the DIFE equation was convenient for popularization and application owing to transforming the subjective clinical factors into objective parameters, especially for non-nephrologist and doctors in primary hospitals. It may be the new standard in the assessment of the timing of dialysis replacing eGFR. To further evaluate the predictive ability and clinical accuracy of DIFE, we designed a prospective multicenter randomized controlled trial from 28 hospitals located in different regions in China to

assess clinical outcomes of ESRD patients, placed in optimal or late start dialysis cohorts on the basis of DIFE. The aims of the trial to assess the effect of the optimal and late start dialysis, based on DIFE, using the 3 years mortality, hospitalization, morbidity, quality of life, and medical costs of hemodialysis patients. The ADIFE study will provide clinical evidence for the optimal time to start dialysis in ESRD patients based on DIFE.

Methods and analysis

Study design

The ADIFE study is a prospective, multicenter, randomized controlled, open-label trial in ESRD patients. which was divided into an "optimal start dialysis" group with DIFE value between 30 and 35 and a "late start dialysis" group with DIFE value less than 30 respectively. The study will be implemented in 28 dialysis centers, covering the seven administrative regions in China (North China, East China, South Central, Northeast, Southwest and Northwest). Each participating center has systemic follow-up for the participants with chronic kidney disease and can afford predialysis care including preparation of vascular access in patients approaching hemodialysis.

Participants will be followed up at baseline, pre-dialysis visiting stage every 12 weeks, and post-dialysis visiting stage every 12 or 24 weeks. The whole trial flow diagram is detailed in Figure 1. The protocol of ADIFE study was designed according to the SPIRIT reporting guidelines[21].

Participants

Inclusion criteria

Participants will enroll the study if they meet all the following requirements

a. Adults age between 18 to 75 years old;
b. Chronic kidney disease with an eGFR (calculated by the CKD-EPI equation[22]) less than 15mL/min/1.73m^2 and the DIFE between 30 and 35;
c. Expected to commence maintenance hemodialysis;
d. Agreeable to randomization.

Exclusion criteria

Participants will be excluded if meet the one of the following items

a. Acute kidney injury (AKI) or AKI on chronic kidney diseases (CKD);
b. With the primary disease of systemic lupus erythematosus（SLE）or systemic vasculitis;
c. Have received or planning to receive a kidney transplantation or peritoneal dialysis;
d. Recently diagnosed cancer that was likely to impact on survival (except for cured cancer or remission for over 5 years, after radical resection of the basal cell carcinoma or squamous carcinoma of skin or carcinoma in-situ of any part of the body);
e. Hepatocirrhosis;
f. Positive test of Human Immunodeficiency Virus (HIV), the hepatitis B virus antigen (HBsAg) or anti-hepatitis C virus antibody (HCV Ab);
g. Acute infection disease within 1 month;
h. Bad habit which is difficult to withdrawal such as alcohol abuse;
i. Poor compliance;
j. Being pregnant, nursing or planing for pregnancy;
k. Life expectancy less than 1 year;
l. The investigator confirm that should not enroll in the study with any other cases.

Sample size

The sample size estimate mainly based on the primary endpoint of the 3 years all-cause mortality On the basis of previous DIFE study with retrospective cohort study, which showed that the 3 years mortality of the optimal start group was 8.38% and that of the late start group was 19.4%. Using the PASS Version 15 of Power and Sample Size Calculation program, Therefore, we estimated a sample size of 154 per group (assuming a type I error rate of 5% with 80% power, two-sided test, with $P<0.05$ considered statistically significant), and assuming that 20% of participants would withdraw or drop out, the target sample size was 388 participants, or 194 participants in each group will be recruited.

Randomization and allocation

Independent biostatisticians with no relationship to the data management and data statistical analysis team will use the SAS 9.2 software (version 9.1.3; SAS Institute,

Inc., Cary, NC, USA) stratified by site to generate random numbers according to the block randomization method. The investigators will allocate the random numbers to eligible participants assigned 1:1 to optimal start dialysis group or late start dialysis group according to the enrollment sequence. Randomization allocation and random number will be sent by automated email, to the non-blind investigators performing the randomization using their unique user name and password on the internet-based randomization service of Randomization and Trial Supply Management system.

Patient and Public Involvement

A patient and public involvement (PPI) reference group comprising dialysis patients, their partners, carers and representatives from Voluntary Sectors will be formed. The PPI reference group will meet quarterly throughout the duration of the program. Group members have been consulted at all stages of the work leading to this proposal, provided valuable insight and advice. The trial was designed in partnership with PPI to help maximizing patient benefits. Our PPI representatives have materially influenced decisions on the study population, promotion and recruitment, they will also continue to contribute throughout this pilot study in terms of reviewing documentation for ethics approval, reading reports and contributing to dissemination activities. We will also present the final results of the ADIFE trial to PPI.

Treatment

All participants receive regular treatment as usual, which include regular dietary advice, anemia and Chronic Kidney Disease-Mineral and Bone Disorder management, blood pressure, and volume control as recommended by the KDIGO guideline and Chinese Hemodialysis Adequacy guidelines[19, 23-26]. Different types of vascular access including temporary venous catheters, arteriovenous fistula, and artificial blood vessel are permitted to be used in all participants. The use of such catheters is based only on clinical requirements. Each participating center has been advised to consider early access creation in each participant to avoid delay in the subsequent hemodialysis treatment.

All participants undergoing hemodialysis treatment with capacity control dialysis machine, bicarbonate dialysate, blood flow volume with 200 ~ 300ml/min, disposable

high-flux or low-flux dialyzer with membrane area 1.3 ~ 1.6m^2, dialysis dose is 4 hours per treatment with 2 or 3 times in one week; and the recommended spKt/V is more than 1.2[19, 26, 27]. However, despite the existence of dialysis management guidelines in China, there is still potential for treatment variation between the participating centers.

Intervention

Participants allocated to the 'optimal start dialysis' group will commence dialysis with the DIFE values between 30 and 35. Participants allocated to the "late start dialysis" group were monitored based on the changes in DIFE values in the pre-dialysis visiting stage every 12 weeks until their DIFE values were less than 30, and then commenced dialysis. Participants allocated to the "late start dialysis" group are able to commence dialysis earlier based on the recommendation of their caring physician although the DIFE no less than 30, for instance, Participants appearing obvious uremia symptoms, volume overload, hyperkalemia and so on, which the reasons for the early initiation of dialysis to be recorded, this will allow for a subsequent analysis of actual DIFE at the dialysis start time.

Outcome measurement

All enrolled participants will be followed up until death or until 144 weeks after the last patient is randomized. Participants with "late start dialysis" group were assessed every 12 weeks in the pre-dialysis visiting stage. During the period of post-dialysis visiting stage, data will be collected every 12 weeks in the first year of follow-up and every 24 weeks in the next two years of follow-up, The detailed follow-up items in different visiting stage showed in table 1.

Comprehensive demographic data (age, gender, ethnicity, height, weight, education, employment, causes of ESRD, medical history, presence of comorbid conditions, collected on all participants at baseline. Virology examination (Hepatitis B virus antigen, hepatitis C virus antibody, human immunodeficiency virus antibody, syphilis antibody), urine human chorionic gonadotropin (HCG) were tested in screening stage, vital signs, which include temperature (T), heart rate (HR), respiratory rate (RR), non-invasive blood presure (BP) were monitored each follow-up. Biochemical indexes including blood cell count (Red Blood Cells, White Blood Cells,

Platelets), hemoglobin (Hb), blood urea nitrogen (BUN), serum creatinine (Scr), eGFR, electrolytes (serum sodium, serum potassium, serum chloride, serum calcium, serum phosphate), alanine transaminase (ALT), glutamic-oxalacetic transaminease (AST), total bilirubin (T-BIL), blood glucose, serum lipid, serum ferrium(SF), parathyroid hormone (PTH), and ferritin were tested every 12-24 weeks in each participating center. Inflammatory biomarkers including high-sensitivity C-reactive protein (hs-CRP), IL-6, IL-10, tumor necrosis factor-α（TNF-α） and β_2-microglobulin（β_2-MG）will be collected and tested every 24 weeks by central lab in the Kidney Disease Research Institute of Dalian Medical University. Nutritional status was assessed using Subjective Global Assessment (SGA)[28] and serum albumin level every 24 weeks. Quality of life will be measured using the well-validated Kidney Disease Quality of Life Short Form™ (KDQOL-SF™)[29, 30] every 48 weeks; and cognitive function will be assessed using the Montreal Cognitive Assessment (MoCA)[31] every 24 weeks. Concomitant medications including calcium channel blockers (CCB), statins, angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), and erythropoiesis stimulating agents (ESAs) are also being collected at baseline and follow-up period. Medical costs will be recorded in pre-dialysis visiting stage and post-dialysis visiting stage by both the questionnaire and medical insurance records of the participants, including dialysis related costs, hospitalization related costs, and outpatient costs of comorbidities treatment.

The all following data will be recorded on standardized online electric case report forms (eCRFs) based on electronic data acquisition system. All adverse events（AE）will be recorded on the eCRFs on specific pages reserved for this purpose. Serious adverse events（SAE）are defined as death, life-threatening, hospitalization (or prolongation of initial hospitalization), cause disability or cause permanent damage, a congenital anomaly, or birth defect. Completed eCRFs entered into a secured central database for independent quality control and centralized analysis.

Table 1 The Follow-up items in different visiting stage of ADIFE study

Follow-up items	Screening stage	Pre-dialysis visiting stage	Post-dialysis visiting stage
			V0~V8（0~144w）

Signed informed consent form	√	-	-
Inclusion and exclusion criteria	√	-	-
Demographic data	√	-	-
Vital signs, physical examination	√	√	√（V0~V8）
Urine HCG	√	-	-
Virology examination	√	-	-
Blood routine test	√	√	√（V0~V8）
BUN, Scr, eGFR, Alb, Electrolytes,	√	√	√（V0~V8）
ALT, AST, T-BIL, Blood glucose, Serum lipid, serum Ferrium	-	-	√（V0、V4、V6、V8）
PTH, Ferritin	-	-	√（V0、V2、V4~V8）
Hs-CRP、IL-6、IL-10、TNF-α、β_2-MG	-	-	√（V0、V2、V4~V8）
KDQoL-SF	-	-	√（V0、V4、V6、V8）
MoCA	-	-	√（V0、V2、V4~V8）
SGA	-	-	√（V0、V2、V4~V8）
Vascular access	-	-	√（V0~V8）
Medical costs	-	√	√（V0~V8）
Complications related to dialysis	-	-	√（V0~V8）
AE、SAE	-	√	√（V0~V8）
Concomitant medications	-	√	√（V0~V8）

Note: "√" represent selected follow-up items; "-" represent not-selected follow-up items.HCG, human chorionic gonadotropin; BUN, blood urea nitrogen; Scr,serum creatinine; eGFR, estimate glomerular filtration rate; ALB, albumin; ALT, alanine transaminase; AST, glutamic-oxalacetic transaminease; T-BIL, total bilirubin; PTH, parathyroid hormone; hs-CRP, high sensitive C-reactive protein; TNF-α, tumor necrosis factor-α; β_2-MG, β_2-microglobulin; KDQOL-SF, Kidney Disease Quality of Life Short Form; MoCA, Montreal Cognitive Assessment; SGA, subjective global assessment; AE, adverse events; SAE, serious adverse events.

Endpoint measurements

The primary endpoint is 3 years all-cause mortality following randomization to "optimal start dialysis" or "late start dialysis" groups. Secondary endpoints include

cerebro-cardiovascular events (nonfatal myocardial infarction, nonfatal stroke, transient ischemic attack, new-onset angina, acute heart failure or severe arrhythmia which should to be hospitalized), infectious complications, hemodialysis complications (including changes of vascular access, vascular access related infection, fluid and electrolyte disorders, and cognitive dysfunction), annual hospitalization (proportion of participants admitted to hospital every year), quality of life, nutrition assessment，cognitive dysfunction and medical costs.

Statistical analysis

For all baseline and outcome variables, the number of available measurements and the number of missing values will be given. All analyses will be conducted according to the intention-to-treat principle[32], that is, all randomised patients will be analysed in the groups to which they were originally allocated, the noncompliance with treatment and other violations of protocol will be measured and reported as ITT effect estimate, we also will performe inverse probability weighting for adjusting selection bias due to attrition[33]. Continuous variables will be checked for normal distribution and presented as the mean and SD or median and IQR as appropriate. Comparison of continuous variables will be performed by using Student t test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables. Categorical variables will be presented as numbers and percentages, and analysed by the Chi-squared test. The primary outcome of the 3 years all-cause mortality will be compared between optimal start and late start groups using the Cochran-Mantel-Haenszel procedure, adjusting for center. Logistics regression model will be performed to adjust for potential confounders, such as age, sex, cause of ESRD, Comorbidity, Complication of dialysis, Dialysis mode, etc. All analyses will be performed using SAS Version 9.2 (SAS Institute Inc, Cary, NC, USA) by the team of statisticians at the Fuwai Hospital, China. All reported *P* values are two-sided and *P* values less than 0.05 will be considered to be significant.

Ethics and dissemination

Ethics

Ethical approval was obtained from the ethics committees of the First Affiliated

Hospital of Dalian Medical University (Registration No:YJ-KY-2017-119), and all participating centers will also obtain additional ethics approval in accordance with local practice.

Informed consent and withdrawal from the study

Each participant or authorised surrogates will sign an informed consent form. The process of informed consent will be in accordance with the Declaration of Helsinki. Participants were fully informed about the ADIFE study by the investigators, and were able to discuss the trial process with their nephrologists and contact the investigator directly to request further information. Participants and authorised surrogates will received the related materials of informed consent. Participants were informed of their right to withdraw from the study either at their own request or at the discretion of the investigator at any time without their care being affected in any way.

Dissemination plan

Survey data will be exported directly from eCRF as a text file and imported in electronic form for scoring and analysis using statistics software. A detailed database will track participants' progress through the trial including the scheduling of assessments and reminders to complete assessments. Detailed strategies, including phone or text message reminders will be used to remind participants about upcoming assessments. All members of the research team and other associated personnel will have access to the final trial dataset in both identified and re-identifiable forms.

Print data will be stored in locked filing cabinets accessible only to the research team. Electronic data will bestored on password-protected computers or servers only accessible to the research team. All paper and electronic records will be retained and disposed of in accordance with the requirements of the Criterions for the Quality Control of Clinical Trial from Drugs China Food and Drug Administration （CFDA）.

Results from the outcome measures will not be presented in a way that adversely affects the confidentiality of participants. The description of participants will not allow identification of individual participants, and individual results and individual names will not be revealed. Final reports and publications will only consist of aggregated

results. At the completion of the study, participants will receive a plain chinese summary of study results. Scientific reports of the main outcomes, secondary outcomes and process evaluation will be submitted to an international peer-reviewed journals. Results will also be presented at national and international conferences relevant to the subject fields.

Data management

All information of participants will be recorded on standardized online electric case report forms (eCRFs) which will be anonymized and saved on password-protected computers. The data monitoring committee (DMC) is independent from the sponsor and competing interests, will meet twice yearly to review the efficacy and safety data.

Oversight committees

A Trial Steering Committee has been set-up and will include an independent chairman, 28 independent members and the study's investigators.

Safety monitoring

AE will be closely monitored. These are events that are likely to affect to a significant degree the safety or physical or mental integrity of the participants in the trial. SAE must be reported to the sponsor (First Affiliated Hospital of Dalian Medical University, China) and the State Food and Drug Administration promptly by fax or telephone by investigators, followed by a written report within 24 hours, The sponsor will be notified immediately of any case where the above definition applies during the trial.

Discussion

The timing of dialysis initiation is a risk factor affecting the prognosis of patients with ESRD. Optimal timing of dialysis initiation remains unclear. Some studies showed early start dialysis was associated with a lower risk of mortality[5] and others studies indicated either a survival advantage of late start dialysis[3, 11, 12, 34] or comparable mortality risk between early and late start dialysis[35, 36]. IDEAL study indicated that using eGFR as the primary guide for when to start dialysis likely should be abandoned in a patient with progressive advanced CKD[10].

The noval DIFE integrate subjective clinical variables of uremic signs and symptoms with objective biochemical markers beyond serum creatinine and eGFR for

assessing timing of dialysis initiation in ESRD patients, which provide a individualized, effective and convenient tool for dialysis initiation decision making. The results of ADIFE study will provide solid evidence for evaluating the accuracy and efficacy of DIFE and maybe provide the potential optimal timing of dialysis initiation with ESRD patients approaching the need for maintenance dialysis. Some nephrologists and non-nephrologis with less trained who may not know how to interpret laboratory values and clinical signs a formula to calculate when to start dialysis can be very helpful to deliver safe care.

The DIFE formula were established through a previous retrospective multicenter cohort study with hemodialysis patients' data, the ADIFE study will further assess the clinical accuracy and availability of DIFE for guiding the timing of hemodialysis initiation, therefore, the ADIFE study excluded the Participants waiting peritoneal dialysis and transplantation, but we have already planned to assess the availability of DIFE for guiding the timing of dialysis with peritoneal dialysis patients through other clinical study.

Author contributors

All authors meet ICMJE criteria for authorship in that they have contributed substantially to the conceptual design or the processes of data collection, analysis or interpretation, the drafts and revisions of the study protocol and manuscript, granted approval of the final version of the study protocol and acknowledged their accountability with regard to the integrity and accuracy of this study protocol.

Research idea and study design: Hongli Lin, Xiangmei Chen, Xuefeng Sun, Ximing Sun, Degang Wang, Ming Fang and Lynda Szczech.

Writing and reviewing of the protocol: Jilin chen, Ying Liu, Hongli Lin, Ping Li and Yang Wang.

Drafting of the manuscript: Jilin chen, Ying Liu and Zach Odeh will be responsible for administrative and managerial procedures related to all phases of the trial, which will be supervised by Hongli Lin.

Statistical analysis: Yang Wang, and Wei Li.

Participants enrollment and follow up related work: Jilin chen, Ying Liu, Hongli Lin,

Hongli Jiang, Wei Shi, Wenhu Liu, Ping Fu, Xiaoqiang Ding, Ming Chang, Shuxin Liu, Xiao Yang, Ning Cao, Menghua Chen, Zhaohui Ni, Jing Chen, Shiren Sun, Xinling Liang, Huimin Wang, Yani He, Bihu Gao, Jianqin Wang, Lirong Hao, Jian Liu, Suhua Li, Qiang He, Hongmei Liu, Na Yi, Fengmin Shao, Jundong Jiao, Yuhuan Ma, Li Yao, Yi Sun and Detian Li.

Trial status

Recruitment will commence using digital social media networks and print-based advertising nationwide in April 2018. Completion of recruitment is expected in December 2018. The study will be completed in December 2021.

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The NHFPC had no role in the design, conduct, management, analysis, or interpretation of the study.

Conflicts of interests None.

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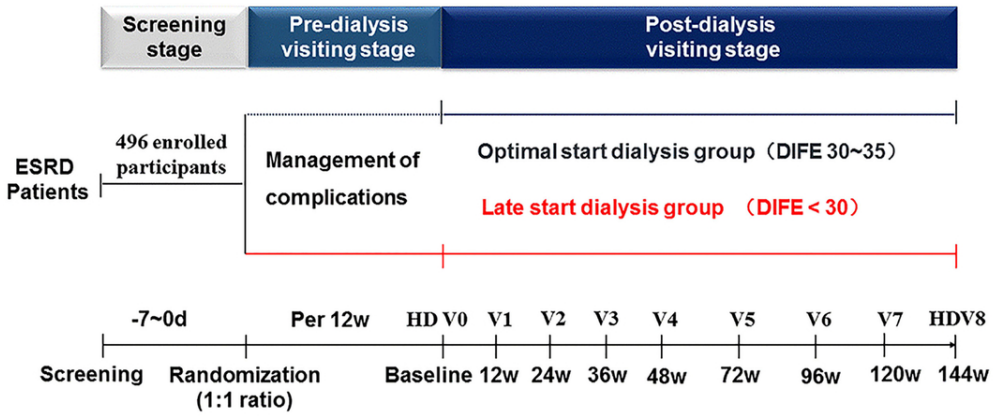
Figure legends

Figure 1 **Trial Flow Diagram of the ADIFE study.** The whole trial flow including the screening stage within seven days, pre-dialysis visiting stage and post-dialysis visiting stage of visit 0 ~ visit 8. Enrolled subjects will be randomised 1:1 to the optimal start dialysis group with DIFE value between 30 and 35 or late start dialysis group with DIFE value less than 30. Participants will be followed up at baseline（visit 0）, pre-dialysis visiting stage every 12 weeks, and post-dialysis visiting stage every 12 or 24 weeks. ESRD, End-Stage Renal Disease; DIFE, Dialysis Initiation based on Fuzzy-mathematics Equation.



Trial Flow Diagram of the ADIFE study

90x40mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	4
Protocol version	#3	Date and version identifier	n/a
Funding	#4	Sources and types of financial, material, and other support	17
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1-3,16
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	15

sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	17
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	15
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-7
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5-7
Objectives	#7	Specific objectives or hypotheses	6-7
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	7
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	9-10
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	9-12
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9-10
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-13
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	14
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed	9

mechanism		envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	15
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13

Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	15
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	15
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	14
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	n/a
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	14
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14-15
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Data access	#29	Statement of who will have access to the final trial dataset,	15

		and disclosure of contractual agreements that limit such access for investigators	
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	14
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

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Assessment of Dialysis Initiation by a Fuzzy mathematics Equation (ADIFE): A study protocol for a randomized controlled trial

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Assessment of Dialysis Initiation by a Fuzzy mathematics Equation (ADIFE): A study protocol for a randomized controlled trial

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ABSTRACT

Introduction Starting dialysis early or late both result in a low quality of life and a poor prognosis in patients undergoing hemodialysis. However, there remains no consensus on the optimal timing of dialysis initiation, mainly because of a lack of suitable methods to assess variations in dialysis initiation time. We have established a novel equation named DIFE (Dialysis Initiation based on Fuzzy-mathematics Equation) through a retrospective, multicenter clinical cohort study in China to determine the most suitable timing of dialysis initiation. The predictors of the DIFE include nine biochemical markers and clinical variables that together influence dialysis initiation. To externally validate the clinical accuracy of DIFE, we designed the ADIFE (assessment of DIFE) study as a prospective, open-label, multicenter, randomized controlled trial to assess the clinical outcomes among patients who initiate dialysis in an optimal start dialysis group and a late start dialysis group, based on DIFE.

Methods and analysis A total of 388 enrolled patients with end-stage renal disease (ESRD) will be randomized 1:1 to the optimal start group, with a DIFE value between 30 and 35, or the late start dialysis group, with a DIFE value less than 30, using the Randomization and Trial Supply Management (RTSM) system. Participants will be assessed for changes in signs and symptoms, dialysis mode and parameters, biochemical and inflammatory markers, Subjective Global Assessment (SGA), Kidney Disease Quality of Life Short Form (KDQOL-SF™), Cognitive Assessment (MoCA), Medical costs, adverse events, and concomitant medication at baseline, pre-dialysis visiting stage and post-dialysis visiting stage, every 12 to 24 weeks. The following data will be recorded on standardized online electric case report forms (eCRFs). The primary endpoint is 3-year all-cause mortality. The secondary endpoints include non-fatal cerebro-cardiovascular events, annual hospitalization rate, quality of life, medical costs, and hemodialysis related complications.

Ethics and dissemination Ethical approval was obtained from the Ethics Committee of the First Affiliated Hospital of Dalian Medical University China (Registration No: YJ-KY-2017-119) and the ethics committees of all participating centers.

The final results of the ADIFE trial will be presented to the study sponsor, clinical researchers, and the patient and public involvement (PPI) reference group. Findings will be disseminated through peer-reviewed journals, Clinical Practice Guidelines, and at scientific meetings.

Trial registration number ClinicalTrial.gov. NCT03385902; Pre-results.

Keywords End-Stage Renal Disease; Hemodialysis; Timing of Dialysis Initiation; Fuzzy mathematics.

STRENGTHS AND LIMITATIONS OF THIS STUDY

► We established a novel and quantifiable equation (DIFE), containing nine laboratory and clinical parameters that together influence the timing of dialysis initiation, which showed significant advantages to assess the timing of dialysis initiation compared with the estimated glomerular filtration rate alone.

► This is the first prospective, randomized controlled study to assess the timing of initiation of dialysis based on DIFE in patients with ESRD.

► The study will provide acceptability and feasibility data for optimal dialysis initiation based on DIFE to avoid early and late start dialysis in patients with ESRD.

► Participants will be recruited from 25 hemodialysis centers in China, which may introduce sample selection bias.

► The hemodialysis centers do not all use the same dialyzers to treat the participants.

INTRODUCTION

The growing prevalence and incidence of end-stage renal disease (ESRD) represents a global health challenge.[1] Hemodialysis is the main treatment for patients with ESRD, and its start time has a significant effect on patient survival.[2-4] Late or early start of dialysis can negatively affect the quality of life and survival prognosis of patients, and this sub-optimal timing of dialysis results in an increased economic burden for families and society.[5-7] Therefore, determining and implementing the optimal time to commence dialysis could improve a patient's quality of life by relieving their uremic symptoms, decreasing their risk of early death, and by reducing medical care costs.[4] However, there is still no consensus on the optimal timing of dialysis initiation for patients with ESRD, and it is unknown what is exactly the optimal timing of dialysis is associated with better outcomes. Several observational studies found that an earlier start of dialysis was associated with improved survival and better prognosis.[5,8,9] However, certain cohort studies and a randomized controlled trial (the Initiating Dialysis Early and Late (IDEAL) study) have shown that patients receiving early initiation of dialysis were at risk of poor survival and that late initiation of dialysis was associated with lower risk of mortality and improved survival.[10-13] However, these findings are controversial mainly because of the inefficient or outdated methods of assessing dialysis timing used. All of the above studies used the creatinine-based estimated glomerular filtration rate (eGFR), a value whose specificity is affected by nutritional status and muscle mass, and is calculated by either the Modified Diet in Renal Disease equation or the Cockcroft–Gault equation.[14,15] Studies have shown that some clinical factors, such as older age, volume overload, malnutrition, diabetes, and heart failure, strongly influence the timing of dialysis initiation.[5,16-18] Therefore, the Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guideline for

Hemodialysis Adequacy recommend that the decision to initiate maintenance dialysis should be based primarily on the assessment of specific complications of kidney disease, including signs and symptoms of uremia, protein-energy wasting, metabolic abnormalities, and volume overload, rather than based on the eGFR alone.[19,20] Deviation from an empirical decision to an assessment of varying clinical conditions inevitably leads to a lack of consensus because of clinicians' subjective judgments, which can lead to a sub-optimal decision regarding early or late initiation of dialysis.

Thus, our research team established a novel equation to determine the optimal timing, called dialysis initiation based on a Fuzzy mathematical method (DIFE), which was derived from a previous multicenter, retrospective cohort study with large-scale samples.[21] The DIFE includes nine parameters: Sex, age, blood urea nitrogen, serum creatinine, hemoglobin, serum albumin, serum phosphorus, heart failure condition, and diabetes condition, which effectively combines subjective clinical variables with objective biochemical markers for dialysis initiation decision making. The DIFE study showed that the 3-year dialysis mortality of patients in the optimal start group (DIFE value of 30 to 35) was markedly lower (8.38%) than the late start group (DIFE value less than 30) of 19.4%. Moreover, receiver operating characteristic (ROC) curve analysis indicated that the area under the curve (AUC) for the prediction of 3-year death during dialysis initiation assessed by the DIFE was significantly higher than that predicted by eGFR (0.70 *vs*. 0.55, $P < 0.01$).[21] Therefore, the DIFE is more accurate and effective to assess the timing of hemodialysis initiation than eGFR alone. Furthermore, the DIFE equation is convenient for popularization and application because it transforms subjective clinical factors into objective parameters, which will be especially appealing to non-nephrologists and doctors in primary hospitals. DIFE may become the new standard in the assessment of the timing of dialysis, replacing eGFR. To further evaluate the predictive ability and clinical accuracy of DIFE, we designed a prospective, multicenter randomized controlled trial, involving 25 hospitals located in different regions in China, to assess clinical outcomes of patients with ESRD placed in optimal or late start dialysis cohorts on the basis of DIFE. The aims of the trial are

to assess the effect of the optimal and late start dialysis, based on DIFE, using the 3-year mortality rate, hospitalization, morbidity, quality of life, and medical costs of patients receiving hemodialysis. We believe that the assessment of DIFE (ADIFE) study will provide clinical evidence for the optimal time to start dialysis in patients with ESRD based on DIFE.

METHODS AND ANALYSIS

Study design

The ADIFE study is a prospective, multicenter, randomized, controlled, open-label trial in patients with ESRD. Patients will be divided into an 'optimal start dialysis' group, with DIFE value between 30 and 35, and a 'late start dialysis' group, with a DIFE value less than 30. The study will be implemented in 25 dialysis centers, covering the seven administrative regions in China (North China, East China, South Central, Northeast, Southwest, and Northwest). Each participating center has a systemic follow-up procedure for the participants with chronic kidney disease and can provide predialysis care including preparation of vascular access in patients approaching hemodialysis.

Participants will be followed up at baseline, at the pre-dialysis visiting stage every 12 weeks, and at the post-dialysis visiting stage every 12 or 24 weeks. A flow diagram of the whole trial is shown in Figure 1. The protocol of the ADIFE study was designed according to the SPIRIT reporting guidelines.[22]

Participants

Inclusion criteria

Participants will be enrolled the study if they meet all the following requirements:

a. Adults age between 18 to 75 years old;
b. Chronic kidney disease with an eGFR (calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation[23]) of less than 15 mL/min/1.73 m^2 and a DIFE value between 30 and 35;
c. Expected to commence maintenance hemodialysis;
d. Agreeable to randomization.

Exclusion criteria

Participants will be excluded if they meet one of the following items:

a. Acute kidney injury (AKI) or AKI on chronic kidney diseases (CKD);
b. Having a primary disease comprising systemic lupus erythematosus (SLE) or systemic vasculitis;
c. Have received, or are planning to receive, a kidney transplantation or peritoneal dialysis;
d. Recently diagnosed cancer that is likely to impact on survival (except for cured cancer or cancer in remission for over 5 years, after radical resection of the basal cell carcinoma or squamous carcinoma of skin or carcinoma in-situ of any part of the body);
e. Hepatocirrhosis;
f. Positive test for Human Immunodeficiency Virus (HIV), hepatitis B virus antigen (HBsAg), or anti-hepatitis C virus antibody (HCVAb);
g. Acute infectious disease within 1 month;
h. Poor lifestyle choice that is difficult to withdraw from, such as alcohol abuse;
i. Poor compliance;
j. Being pregnant, nursing, or planning for pregnancy;
k. Life expectancy less than 1 year;
l. Other cases in which the investigator confirms that they should not enroll in the study.

Sample size

The sample size estimate is mainly based on the primary endpoint of the 3-year all-cause mortality from the previous retrospective cohort DIFE study, which showed that the 3-year mortality of the optimal start group was 8.38% and that of the late start group was 19.4%.[21] Using PASS Version 15 of the Power and Sample Size Calculation program (NCSS, LLC, Kaysville, Utah, USA), we estimated a sample size of 154 per group (assuming a type I error rate of 5% with 80% power, two-sided test, with $P < 0.05$ considered statistically significant). Assuming that 20% of the participants would withdraw or drop out, the target sample size was estimated as 388 participants, meaning that 194 participants in each group will be recruited.

Randomization and allocation

Independent biostatisticians with no relationship to the data management or the data statistical analysis team will use the SAS 9.2 software (version 9.1.3; SAS Institute, Inc., Cary, NC, USA) stratified by site to generate random numbers according to the block randomization method. The investigators will allocate the random numbers to eligible participants, assigned 1:1 to the optimal start dialysis group or the late start dialysis group, according to the enrollment sequence. Randomization allocation and random numbers will be sent by automated email to the non-blind investigators performing the randomization using their unique user name and password on the internet-based randomization service of a Randomization and Trial Supply Management system.

Patient and Public Involvement

A patient and public involvement (PPI) reference group, comprising dialysis patients, their partners, carers, and representatives from voluntary sectors, will be formed. The PPI reference group will meet quarterly throughout the duration of the program. Group members have been consulted at all stages of the work leading to this proposal, and have provided valuable insight and advice. The trial was designed in partnership with the PPI to help maximize patient benefits. Our PPI representatives have materially influenced decisions on the study population, promotion, and recruitment. They will also continue to contribute throughout this pilot study in terms of reviewing documentation for ethics approval, reading reports, and contributing to dissemination activities. We will also present the final results of the ADIFE trial to the PPI.

Treatment

All participants will receive regular treatment as usual, which includes regular dietary advice, anemia and Chronic Kidney Disease-Mineral and Bone Disorder management, blood pressure, and volume control, as recommended by the KDIGO guidelines and the Chinese Hemodialysis Adequacy guidelines.[19,24-27] Different types of vascular access, including temporary venous catheters, arteriovenous fistulas, and artificial blood vessels are permitted for use in all participants. The use of such catheters will be based only on clinical requirements. Each participating center has

been advised to consider early access creation in each participant to avoid delay in the subsequent hemodialysis treatment.

All participants will undergo hemodialysis treatment using capacity control dialysis machines, bicarbonate dialysate, a blood flow volume of 200–300 mL/min, and a disposable high-flux or low-flux dialyzer with membrane area of 1.3–1.6 m^2. The dialysis dose is 4 hours per treatment, performed 2 or 3 times per week; and the recommended single pool Kt/V (spKt/V) is more than 1.2.[19,27,28] However, despite the existence of dialysis management guidelines in China, there is still a potential for treatment variation between the participating centers.

Intervention

Participants allocated to the 'optimal start dialysis' group will commence dialysis when their DIFE values are between 30 and 35. Participants allocated to the 'late start dialysis' group will be monitored based on the changes in DIFE values in the pre-dialysis visiting stage every 12 weeks until their DIFE values are less than 30, and then dialysis will commence. Participants allocated to the 'late start dialysis' group will be able to commence dialysis earlier based on the recommendation of their caring physician, although they should have a DIFE value of no less than 30. For instance, participants showing obvious uremia symptoms, volume overload, and hyperkalemia, for which the reasons for early initiation of dialysis will be recorded; this will allow for a subsequent analysis of actual DIFE at the dialysis start time.

Outcome measurement

All enrolled participants will be followed up until death or until 144 weeks after the last patient is randomized. Participants in the 'late start dialysis' group will be assessed every 12 weeks in the pre-dialysis visiting stage. During the post-dialysis visiting period, data will be collected every 12 weeks in the first year of follow-up and every 24 weeks in the next two years of follow-up. The detailed follow-up items in different visiting stage are shown in table 1.

Comprehensive demographic data (age, gender, ethnicity, height, weight, education, employment, causes of ESRD, medical history, presence of comorbid conditions) will be collected for all participants at baseline. Virology examination

(Hepatitis B virus antigen, hepatitis C virus antibody, human immunodeficiency virus antibody, syphilis antibody) and human urine chorionic gonadotropin (HCG) will be tested in the screening stage. Vital signs, including temperature (T), heart rate (HR), respiratory rate (RR), and non-invasive blood pressure (BP) will be monitored at each follow-up. Biochemical indexes, including blood cell count (red blood cells, white blood cells, and platelets), hemoglobin (Hb), blood urea nitrogen (BUN), serum creatinine (Scr), eGFR, electrolytes (serum sodium, serum potassium, serum chloride, serum calcium, and serum phosphate), alanine transaminase (ALT), glutamic-oxaloacetic transaminease (AST), total bilirubin (T-BIL), blood glucose, serum lipid, serum iron, parathyroid hormone (PTH), and ferritin will be tested every 12–24 weeks in each participating center. Inflammatory biomarkers, including high-sensitivity C-reactive protein (hs-CRP), interleukin (IL)-6, IL-10, tumor necrosis factor-α (TNF-α), and β_2-microglobulin (β_2-MG), will be tested every 24 weeks by the central laboratory in the Kidney Disease Research Institute of Dalian Medical University. Nutritional status, assessed using Subjective Global Assessment (SGA),[29] and the serum albumin level, will be assessed every 24 weeks. Quality of life will be measured using the well-validated Kidney Disease Quality of Life Short Form™ (KDQOL-SF™)[30,31] every 48 weeks; and cognitive function will be assessed using the Montreal Cognitive Assessment (MoCA)[32] every 24 weeks. The use of concomitant medications, including calcium channel blockers (CCB), statins, angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), and erythropoiesis stimulating agents (ESAs) will be recorded at baseline and during the follow-up period. Medical costs will be recorded in the pre-dialysis visiting stage and post-dialysis visiting stage using both the questionnaire and medical insurance records of the participants, including dialysis-related costs, hospitalization-related costs, and outpatient costs of comorbidities treatment.

All the above-mentioned data will be recorded on standardized online electric case report forms (eCRFs) based on an electronic data acquisition system. All adverse events (AEs) will be recorded on the eCRFs on specific pages reserved for this purpose. Serious adverse events (SAEs) are defined as death, life-threatening illness,

hospitalization (or prolongation of initial hospitalization), causing disability or permanent damage, a congenital anomaly, or a birth defect. Completed eCRFs will be entered into a secured central database for independent quality control and centralized analysis.

Table 1 The Follow-up items in different visiting stage of ADIFE study

Follow-up items	Screening stage	Pre-dialysis visiting stage	Post-dialysis visiting stage
			V0–V8（0–144w）
Signed informed consent form	√	-	-
Inclusion and exclusion criteria	√	-	-
Demographic data	√	-	-
Vital signs, physical examination	√	√	√（V0–V8）
Urine HCG	√	-	-
Virology examination	√	-	-
Blood routine test	√	√	√ (V0–V8)
BUN, Scr, eGFR, Alb, Electrolytes,	√	√	√ (V0–V8)
ALT, AST, T-BIL, Blood glucose, Serum lipid, serum iron	-	-	√ (V0, V4, V6, V8)
PTH, Ferritin	-	-	√ (V0, V2, V4–V8)
Hs-CRP, IL-6, IL-10, TNF-α, β_2-MG	-	-	√ (V0, V2, V4–V8)
KDQoL-SF	-	-	√ (V0, V4, V6, V8)
MoCA	-	-	√ (V0, V2, V4–V8)
SGA	-	-	√ (V0, V2, V4–V8)
Vascular access	-	-	√ (V0–V8)
Medical costs	-	√	√ (V0–V8)
Complications related to dialysis	-	-	√ (V0–V8)
AEs, SAEs	-	√	√ (V0–V8)
Concomitant medications	-	√	√ (V0–V8)

Note: '√' represent selected follow-up items; '-' represent not-selected follow-up items. HCG, human chorionic gonadotropin; BUN, blood urea nitrogen; Scr, serum creatinine; eGFR, estimated glomerular filtration rate; ALB, albumin; ALT, alanine transaminase; AST, glutamic-oxaloacetic transaminase; T-BIL, total bilirubin; PTH, parathyroid hormone; hs-CRP, high sensitive C-reactive protein; IL, interleukin; TNF-α, tumor necrosis factor-α;

β_2-MG, β_2-microglobulin; KDQOL-SF, Kidney Disease Quality of Life Short Form; MoCA, Montreal Cognitive Assessment; SGA, subjective global assessment; AEs, adverse events; SAEs, serious adverse events.

Endpoint measurements

The primary endpoint is the 3-year all-cause mortality following randomization to the 'optimal start dialysis' or 'late start dialysis' groups. Secondary endpoints include cerebro-cardiovascular events (non-fatal myocardial infarction, non-fatal stroke, transient ischemic attack, new-onset angina, acute heart failure, or severe arrhythmia requiring hospitalization), infectious complications, hemodialysis complications (including changes of vascular access, vascular access related infection, fluid and electrolyte disorders, and cognitive dysfunction), annual hospitalization (proportion of participants admitted to hospital every year), quality of life, nutrition assessment, cognitive dysfunction, and medical costs.

Statistical analysis

For all baseline and outcome variables, the number of available measurements and the number of missing values will be recorded. All analyses will be conducted according to the intention-to-treat (ITT) principle,[33] that is, all randomized patients will be analyzed in the groups to which they were originally allocated, and noncompliance with treatment and other violations of the protocol will be measured and reported as an ITT effect estimate. We also will perform inverse probability weighting (IPW) to adjust the selection bias due to attrition.[34] Continuous variables will be checked for normal distribution and will be presented as the mean and SD or median and interquartile range (IQR) as appropriate. Comparisons of continuous variables will be performed using Student's t test for normally distributed variables and the Mann–Whitney U test for non-normally distributed variables. Categorical variables will be presented as numbers and percentages, and analyzed using the Chi-squared test. The primary outcome of 3-year all-cause mortality will be compared between the optimal start and late start groups using the Cochran–Mantel–Haenszel procedure, adjusting for center. A logistics regression model will be performed to adjust for potential confounders, such as age, sex, body mass index (BMI), urine volume, SGA,

blood urea nitrogen, serum creatinine, hemoglobin, serumebumin, serum phosphorus, PTH, Ferritin, Hs-CRP, IL-6, IL-10, TNF-α, β_2-MG, cause of ESRD, vascular access, comorbidity, complication of dialysis, and dialysis mode. All analyses will be performed using SAS Version 9.2 (SAS Institute Inc., Cary, NC, USA) by the team of statisticians at the Fuwai Hospital, China. All reported *P* values will be two-sided and *P* values less than 0.05 will be considered significant.

ETHICS AND DISSEMINATION

Ethics

Ethical approval was obtained from the ethics committees of the First Affiliated Hospital of Dalian Medical University (Registration No: YJ-KY-2017-119) and the ethics committees of all participating centers (see supplementary file).

Informed consent and withdrawal from the study

Each participant or their authorized surrogates will sign an informed consent form. The process of informed consent will be in accordance with the Declaration of Helsinki. Participants will be fully informed about the ADIFE study by the investigators, and will be able to discuss the trial process with their nephrologists and contact the investigator directly to request further information. Participants and authorized surrogates will receive the related materials of informed consent. Participants will be informed of their right to withdraw from the study, either at their own request or at the discretion of the investigator, at any time without their care being affected in any way.

Dissemination plan

Survey data will be exported directly from the eCRFs as a text file and imported in electronic form for scoring and analysis using statistics software. A detailed database will track participants' progress through the trial, including the scheduling of assessments and reminders to complete assessments. Detailed strategies, including phone or text message reminders, will be used to remind participants about upcoming assessments. All members of the research team and other associated personnel will have access to the final trial dataset in both identified and re-identifiable forms.

Printed data will be stored in locked filing cabinets, accessible only to the

research team. Electronic data will be stored on password-protected computers or servers that are only accessible to the research team. All paper and electronic records will be retained and disposed of in accordance with the requirements of the Criteria for the Quality Control of Clinical Trial from Drugs China Food and Drug Administration (CFDA).

The results from the outcome measures will not be presented in a way that compromises the confidentiality of the participants. Descriptions of participants will not allow identification of individual participants, and individual results and individual names will not be revealed. Final reports and publications will only comprise aggregated results. At completion of the study, participants will receive a plain text summary of the study results in Chinese. Scientific reports of the main outcomes, secondary outcomes, and process evaluation will be submitted to an international peer-reviewed journal. The results will also be presented at national and international conferences relevant to the subject fields.

Data management

All information concerning the participants will be recorded on standardized online eCRFs, which will be anonymized and saved on password-protected computers. The data monitoring committee (DMC), which will be independent from the sponsor and any other competing interests, will meet twice yearly to review the efficacy and safety data.

Oversight committees

A Trial Steering Committee has been set-up and will include an independent chairperson, 25 independent members, and the study investigators.

Safety monitoring

AEs will be closely monitored. These are events that are likely to affect the safety or physical or mental integrity of the participants in the trial to a significant degree. SAEs must be reported to the sponsor (the First Affiliated Hospital of Dalian Medical University, China) and the State Food and Drug Administration promptly, by fax or telephone, by the investigators, followed by a written report within 24 hours. The sponsor will be notified immediately of any case where the above definition applies

during the trial.

DISCUSSION

The timing of dialysis initiation is a risk factor that affects the prognosis of patients with ESRD. However, the optimal timing of dialysis initiation remains unclear. Some studies showed that an early start of dialysis was associated with a lower risk of mortality,[5] whereas others studies indicated either a survival advantage of late start dialysis[3,11,12,35] or comparable mortality risk between early and late start dialysis.[36,37] The IDEAL study indicated that using eGFR as the primary guide for when to start dialysis should probably be abandoned in a patient with progressive advanced CKD.[10]

The novel DIFE score integrates subjective clinical variables of uremic signs and symptoms with objective biochemical markers beyond serum creatinine and eGFR to assess the timing of dialysis initiation in patients with ESRD, providing an individualized, effective, and convenient tool for dialysis initiation decision-making. The results of ADIFE study will provide evidence to evaluate the accuracy and efficacy of DIFE and should indicate optimal timing of dialysis initiation for patients with ESRD approaching the need for maintenance dialysis. For some nephrologists and non-nephrologists with less training who may not know how to interpret laboratory values and clinical signs, a formula to calculate when to start dialysis could help them to deliver safe care.

The DIFE formula was established via a previous retrospective multicenter cohort study using data from patients receiving hemodialysis, and the ADIFE study will further assess the clinical accuracy and applicability of DIFE to guide the timing of hemodialysis initiation. Therefore, the ADIFE study will exclude participants awaiting peritoneal dialysis and transplantation; however, we have already planned to assess the applicability of DIFE to guide the timing of dialysis for patients undergoing peritoneal dialysis in another clinical study.

Author contributions

All authors meet the ICMJE criteria for authorship in that they have contributed substantially to the conceptual design or the processes of data collection, analysis, or interpretation, the drafts and revisions of the study protocol and manuscript, granted

approval of the final version of the study protocol, and acknowledged their accountability with regard to the integrity and accuracy of this study protocol.

Research idea and study design: Hongli Lin, Xiangmei Chen, Xuefeng Sun, Ximing Sun, Degang Wang, Ming Fang, and Lynda Szczech.

Writing and reviewing of the protocol: Jilin Chen, Ying Liu, Hongli Lin, Ping Li, and Yang Wang.

Drafting of the manuscript: Jilin Chen, Ying Liu, and Zach Odeh will be responsible for administrative and managerial procedures related to all phases of the trial, which will be supervised by Hongli Lin.

Statistical analysis: Yang Wang, and Wei Li.

Discussion of the protocol or participant enrollment or follow up-related work: Jilin Chen, Ying Liu, Hongli Lin, Hongli Jiang, Wei Shi, Wenhu Liu, Ping Fu, Xiaoqiang Ding, Ming Chang, Shuxin Liu, Xiao Yang, Ning Cao, Menghua Chen, Zhaohui Ni, Jing Chen, Shiren Sun, Xinling Liang, Huimin Wang, Yani He, Bihu Gao, Jianqin Wang, Lirong Hao, Jian Liu, Suhua Li, Qiang He, Hongmei Liu, Na Yi, Fengmin Shao, Jundong Jiao, Yuhuan Ma, Li Yao, Yi Sun and Detian Li.

Trial status

Recruitment has commenced using digital social media networks and print-based advertising nationwide in April 2018. Completion of recruitment is expected in April 2020. The study will be completed by December 2023.

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The NHFPC will have no role in the design, conduct, management, analysis, or

interpretation of the study.

Conflicts of interests None.

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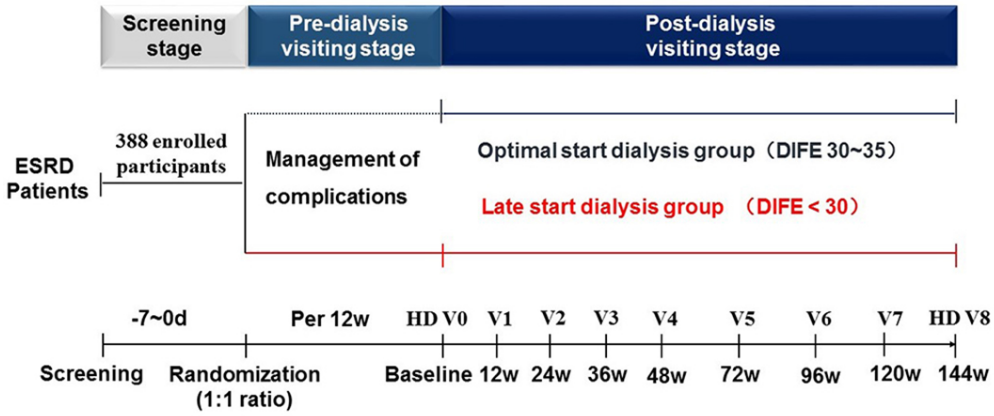
Figure legends

Figure 1 **Trial Flow Diagram of the ADIFE study.** The whole trial flow, including the screening stage within seven days, pre-dialysis visiting stage, and post-dialysis visiting stage of visit 0 to visit 8. Enrolled subjects will be randomized 1:1 to the optimal start dialysis group with a DIFE value between 30 and 35 or to the late start dialysis group with a DIFE value less than 30. Participants will be followed up at baseline (visit 0), pre-dialysis visiting stage every 12 weeks, and post-dialysis visiting stage every 12 or 24 weeks. ESRD, End-Stage Renal Disease; DIFE, Dialysis Initiation based on Fuzzy-mathematics Equation.



Trial Flow Diagram of the ADIFE study

90x40mm (300 x 300 DPI)

The ethics committees of all participating centers

The ethics committees of the First Affiliated Hospital of Dalian Medical University (Registration No: YJ-KY-2017-119) .

The ethics committees of the Chinese PLA General Hospital (Registration No: S2018-021-01).

The ethics committees of the first Affiliated Hospital of Xi'an Jiaotong University (Registration No: XJTU1AF2018LSK-05).

Research Ethics Committee of Guangdong General Hospital, Guangdong Academy of Medical Sciences (Registration No: GDREC2018001H [R1]).

The ethics committees of the Beijing Friendship Hospital, Capital Medical University (Registration No: 2018-P2-013-02).

The ethics committees of the West China Hospital of Sichuan University (Registration No: 2018[39]).

The ethics committees of the Zhongshan Hospital, Fudan University (Registration No: B2018-109R).

The ethics committees of the Dalian Municipal Central Hospital (Registration No: 2018-051-01).

ICE for Clinical Research and Animal Trials of the First Affiliated Hospital, Sun Yat-sen University (Registration No:[2018]021).

The ethics committees of the General Hospital of Ningxia Medical University (Registration No: 2018-137).

Renji Hospital Ethics Committee of Shanghai Jiaotong University School of Medicine (Registration No: [2017]239).

The ethics committees of the Huashan Hospital, Fudan University (Registration No:[2018]013).

The ethics committees of the Xijing Hospital, The Fourth Military Medical University (Registration No: KY20182007-1).

The ethics committees of the General Hospital of Benxi Iron and Steel Co., Ltd (Registration No: No applicable).

The ethics committees Daping Hospital Affiliated to Army Military Medical University (Registration No: [2018]20).

The ethics committees of Affiliated Zhong Shan Hospital of Dalian University (Registration No: 2018-001).

The ethics committees of Lanzhou University Second Hospital (Registration No: 2018A-006).

The ethics committees of the First Affiliated Hospital of Harbin Medical University (Registration No: 201811).

The ethics committees of the First Affiliated Hospital of Xinjiang Medical University (Registration No: 20180330-09).

The ethics committees of the An Steel Group Hospital (Registration No: [2018]3).

The ethics committees of the Henan Provincial People's Hospital (Registration No: [2018]04).

The ethics committees of the Second Affiliated Hospital of Harbin Medical University (Registration No: KY2017-269).

The ethics committees of the General Hospital of Mining Industry Group FuXin (Registration No: Not applicable).

The ethics committees of the First Hospital of China Medical University (Registration No: [2018] 2018-29-2).

The ethics committees of the Central Hospital Affiliated To Shenyang Medical College (Registration No: Not applicable).

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	4
Protocol version	#3	Date and version identifier	n/a
Funding	#4	Sources and types of financial, material, and other support	17
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1-3,16
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	15

sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	17
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	15
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-7
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5-7
Objectives	#7	Specific objectives or hypotheses	6-7
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	7
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	9-10
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	9-12
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9-10
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-13
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	14
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed	9

mechanism		envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	15
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13

Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	15
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	15
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	14
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	n/a
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	14
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14-15
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Data access	#29	Statement of who will have access to the final trial dataset,	15

		and disclosure of contractual agreements that limit such access for investigators	
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	14
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a