APPLICATION VALUE OF REAL-TIME SHEAR WAVE ELASTOGRAPHY IN EVALUATING EFFICACY AND PROGNOSIS OF PATIENTS WITH END-STAGE RENAL DISEASE

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ABSTRACT

Introduction: *Chronic kidney disease is one of the main causes of end-stage renal disease (ESRD) and has a very high mortality rate worldwide. Early assessment of chronic kidney disease is of great significance to the treatment of the disease, and is also the key to protecting the life and health of patients. To explore the application value of real-time shear wave elastography (RT-SWE) in evaluating the efficacy and prognosis of patients with end-stage renal disease (ESRD).*

Materials and methods: *One hundred and thirty-one patients with chronic kidney disease treated in Affiliated Hospital of Hebei University from October 2019 to February 2021 were collected, development of 67 patients with ESRD (observation group, OG), the other 64 cases of chronic kidney disease alone (control group, CG). The modulus of elasticity (MOE) was compared between the two groups, and the clinical significance of MOE and its relationship with the prognosis of patients were analyzed.*

Results: *The MOE of the OG increased, and the MOE of the improvement group decreased ($P<0.05$). Higher 3- and 5-year survival in patients with low MOE values, compared with those with high MOE values ($P<0.05$). The MOE value has a good predictive value for ESRD and the prognostic survival of patients ($P<0.05$).*

Conclusion: *RT-SWE effectively evaluates and predicts the treatment effect and prognosis of patients with ESRD, which may be a candidate application index.*

Keywords: *Real-time shear wave elastic imaging technology, chronic kidney disease, end-stage renal disease, modulus of elasticity.*

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Introduction

Chronic kidney disease (CKD) afflicts approximately 10% of the world's adult population and is the top 20 causes of death worldwide[(1)]. As the disease progresses and severe kidney damage occurs, it will eventually develop into end-stage renal disease (ESRD)[(2, 3)]. Such patients present with a significant decrease in their blood purification ability, leading to a sharp deterioration of renal function, acid-base and water-electrolyte imbalance, entailing renal replacement therapy to maintain their life[(4, 5)]. Therefore, it is necessary to find a feasible way to evaluate the treatment effect and prognosis of patients with ESRD to adjust the specific treatment plan. Ultrasonic elastography is a relatively new ultrasonic imaging technology. Compared with traditional ultrasonic testing, this technology allows for better detection of the elastic changes of tissues[(6)]. Real-time shear wave elastography (RT-SWE), a member of the ultrasonic elastography technology, is not only a non-invasive and painless procedure but also features prominently in objective quantification and rapid imaging, which can accurately measure the elasticity of biological tissues[(7)]. In the past, the most common tests for kidney diseases were urine

protein levels, serum creatinine (Scr) levels, and kidney biopsy[8,9]. However, it has been mentioned in previous studies that although biochemical indexes such as urinary protein and Scr are very convenient to detect, the detection was low in accuracy for some kidney diseases[10]. Renal needle biopsy is an invasive approach that contributes to high accuracy but is unsuitable for primary screening; Moreover, it may lead to complications such as bleeding and arteriovenous fistula and is difficult to be applied repeatedly, which is not conducive to observing the therapeutic efficacy and prognosis of patients at any time[11]. Besides, previous literature has revealed that histopathology often affects tissue elasticity[12].

RT-SWE applies the "Mach cone" effect and uses the probe radiation pulse control technology to make the tissue particles in the focus area generate shear waves due to high-efficiency vibration. With the help of ultra-high-speed imaging technology, the shear wave velocity is detected, and the tissue Young's modulus value is obtained by quantitative analysis. Young's modulus obtained according to the measured renal hardness can better reflect the early fibrosis changes of the kidney since the propagation speed of the shear wave in different tissues is different. Compared with traditional ultrasound and other imaging technologies, RT-SWE is a new concept for evaluating tissue stiffness.

It overcomes the influence of human factors such as the pressure and frequency of the static (quasi-static) elastography probe, and has repetitive features. The advantages of good sex, fast, and no patience[13]. RT-SWE makes the ultrasound elastography technology more perfect, and has shown effectiveness and superiority in many fields. It is believed that this technology can help physicians understand tissue characteristics and pathological conditions in future clinical work, and realize tissue characterization research.

However, the RT-SWE employment on efficacy and prognosis evaluation of patients with ESRD is challenging to track in the existing literature. Therefore, we probed into the clinical value of RT-SWE in patients with ESRD to provide the basis and direction for clinical practice.

Materials and methods

Patient clinical data

A total of 131 patients with CKD treated in Affiliated Hospital of Hebei University from October 2019 to February 2021 were collected, of which 67 patients (41 males and 26 females, mean age 51.3±6.4 years) developed into ESRD were included in the observation group (OG) of this study, and the remaining 64 patients (37 males and 26 females, average age 52.7±6.2 years) who did not developed into ESRD were selected as the control group (CG). The internal Medical Ethics Committee approved the study, and all patients were informed and signed an informed consent form.

Eligibility criteria

Inclusion criteria:

• All patients were diagnosed as CKD based on imaging and pathology[14];

• Have not had any dialysis treatment;

• Expected survival> 2 months;

• Have complete clinical data;

• Prognostic follow-up can be conducted over the phone;

Exclusion criteria:

• Patients with other liver and kidney diseases or malignancies;

• Patients with severe cardiovascular and cerebrovascular diseases/inflammation/immune deficiency;

• Patients during pregnancy or breastfeeding.

RT-SWE detection

Patients were kept on an empty stomach on the day of testing (12h) and were placed in the supine position after urination. The test was performed using the SuperSonic imagine Aixplorer color ultrasound System. All patients were examined by two-dimensional ultrasound, and their kidney conditions were observed through longitudinal section scanning of the kidney.

When the images were stable, Young's modulus of renal parenchyma was detected by RT-SWE. A convex array probe (frequency 3.5-5.5MHz) was placed on the maximum coronal section of the left kidney. The examinee was required to hold the breath for 3-5 s for imaging, and the sampling location was selected in the middle cortical region of the kidney.

The square of the elastography frame was placed into the renal parenchyma and adjusted to the smallest circle. The diameter of the Q-box was adjusted to 8.0-9.0mm, and the Q-box was moved into the renal parenchyma. A total of 5 measurements were made, and the values were recorded and averaged (Figure 1). The same operator performed all testing procedures.

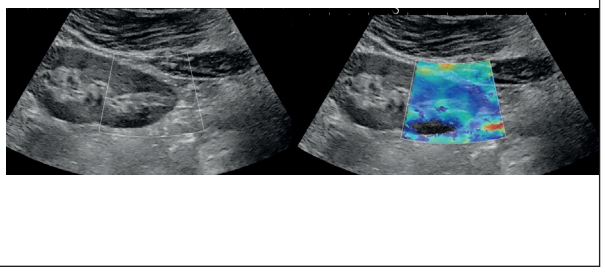

Figure 1: RT-SWE.

Treatment of ESRD

An imported hemodialyzer was used for hemodiafiltration.

The dialysis surface area was 1.3m2, the dialysis frequency was 2-3 times per week (3-4 h/time), and the blood flow was 200-250 mL/min. Treatment improvement was defined as a decrease in Scr by more than 50%, a negative urine protein test result, and normal serum albumin; otherwise, it was evaluated as deterioration[15].

Statistical methods

The collected data were statistically analyzed using SPSS 20.0 (Chicago SPSS Company, the United States). Chi-square test (denoted by X^2) was utilized to analyze the categorical variables expressed as percentages (%); All conforming to the normal distribution, the continuous variables were described as mean±SD and compared by independent samples t-test, with P<0.05 as the level of significance.

The value of RT-SWE in the diagnosis, curative effect and prognosis of patients with ESRD employed receiver operating characteristic (ROC) curves. The 3-year survival of patients was visualized by K-M curves and compared using the Log rank test.

Results

Baseline data

In OG (n=67), there were 41 males and 26 females, with an average age of 51±6.4 years and an average course of disease of 4.3±1.5 years. The male to female ratio in CG (n=64) was 37:27, the mean age was 52.7±6.2 years and the average course of the disease was 4.5±1.7 years.

The comparison of patients' baseline data revealed no statistical difference in age, course of the disease, sex, BMI, diabetes, smoking history, alcoholism history and residence between the two cohorts (P>0.05) Table 1.

		Observation group (n=67)	Control group (n=64)	t/χ^2	P
Age		51.3±6.4	52.7±6.2	1.271	0.206
Course of disease (years)		4.3±1.5	4.5±1.7	0.715	0.476
Gender				0.155	0.694
	Male	41 (61.19)	37 (57.81)		
	Female	26 (38.81)	27 (42.19)		
BMI (kg/m^2)		22.41±1.72	22.05±1.84	1.157	0.249
Diabetes				0.317	0.573
	Yes	13 (19.40)	15 (23.44)		
	No	54 (80.60)	49 (76.56)		
Smoking				2.211	0.137
	Yes	15 (22.39)	8 (12.50)		
	No	52 (77.61)	56 (87.50%)		
Drinking				0.440	0.507
	Yes	5 (7.46)	3 (4.69)		
	No	62 (92.54)	61 (95.31)		
Place of residence				1.681	0.195
	City	48 (71.64)	39 (60.94)		
	Rural	19 (28.36)	25 (39.06)		

Table 1: Patient baseline data.

Modulus of elasticity (MOE) of patients with CKD and its diagnostic significance

Notably, higher MOE values were determined in OG compared with CG (P<0.05, Figure 2-A). Then we used the ROC curve to evaluate the value of MOE in the diagnosis of ESRD in CKD patients, and found that the area under the curve (AUC), 95% confidence interval (CI), specificity, sensitivity and cut-off were 0.880, 0.822-0.938, 82.09, 84.38, and 4.725% respectively, indicating that MOE was of good diagnostic value in diagnosing ESRD in CKD patients (Figure 2-B).

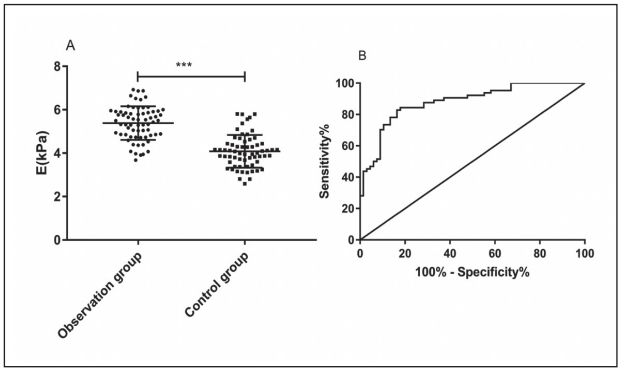

Figure 2: MOE of patients with CKD and its diagnostic significance.

*A. MOE values of patients in the observation group were significantly higher than those in the control group. ***P<0.001. B. ROC curve of MOE in diagnosing ESRD in patients with CKD.*

Diagnostic value of RT-SWE for the efficacy of ESRD

Then, according to the therapeutic efficacy of ESRD patients, we divided them into the improvement group (n=42) and the deterioration group (n=25). Evidently, higher MOE values were identified in the improvement group compared with the deterioration group (Figure 3-A, P<0.05). ROC curves were utilized to evaluate the efficacy of MOE in diagnosing ESRD.

It was found that the AUC, 95%CI, specificity, sensitivity and cut-off were 0.781, 0.658-0.904, 83.33, 72.00, and 5.757% respectively, suggesting that MOE can be used to diagnose the therapeutic efficacy of patients with ESRD (Figure 3-B).

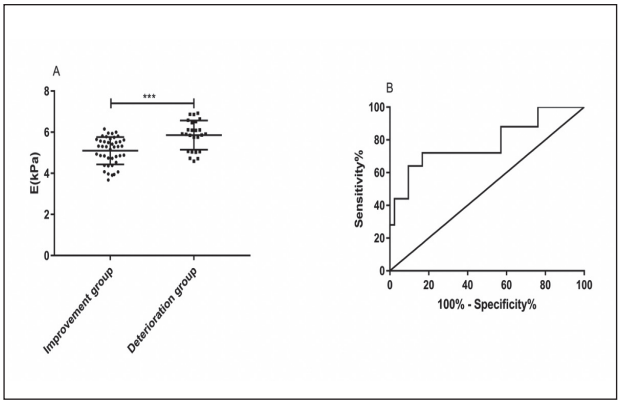

Figure 3: Diagnostic value of RT-SWE for the efficacy of ESRD.
*A. MOE values of patients in the improvement group were significantly lower than those in the deterioration group. ***P<0.001. B. ROC curve for the diagnosis of therapeutic efficacy of ESRD by MOE.*

Prognosis of patients with ESRD

The 3- and 5-year survival of all ESRD patients were counted.

Further, the patients were divided into high- and low-MOE groups according to the median MOE value to compare their survival and prognosis. Markedly higher 3- and 5-year survival rates were determined in the low MOE group compared with the high MOE group. And similar results were demonstrated by K-M curves (Figure 4-A, B, P<0.05).

Subsequently, ROC curves were drawn to detect the 3- and 5-year survival of ESRD patients. It was found that the AUC, 95%CI, specificity, sensitivity and cut-off of MOE for predicting 3-year survival were 0.780, 0.641-0.919, 68.33, 90.91, and 6.049 (Figure 4-C), while those for predicting 5-year survival were 0.856, 0.767-0.945, 68.00, 83.33, and 5.763% (Figure 4-D%), respectively.

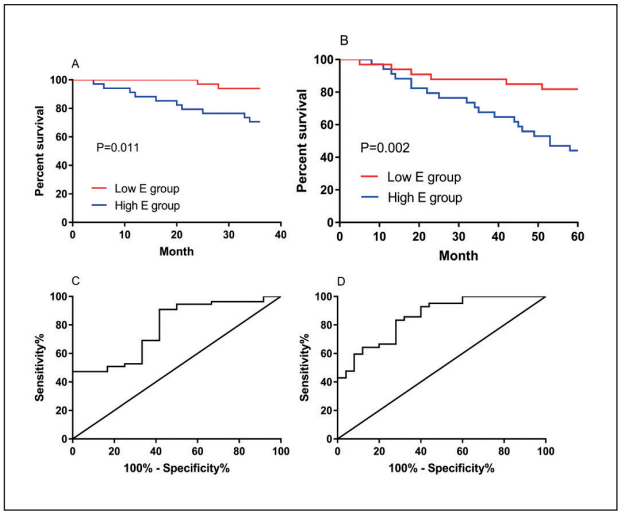

Figure 4: Prognosis of patients with ESRD.
A-B. K-M curves of 3- and 5-year survival of high- and low-MOE groups. C-D. ROC curves of MOE for predicting 3- and 5-year survival of patients with ESRD.

Discussion

The action mechanism of RT-SWE is to apply extra excitation to the tissue by emitting an external or internal static or dynamic acoustic radiation, thus generating shear waves with sufficient strength in the tissue. The organ or tissue to be examined follows the physical effects such as biomechanics and elasticity and quickly produces corresponding responses like tissue displacement changes.

Then using the ultrasonic imaging method, the ultra-high-speed imaging system captures and tracking shear wave imaging system, as well as the digital signal processing technology, the internal changes of the tissue to be examined, are estimated, which directly or indirectly reflects the changes of the MOE value of the tissue to be examined, and finally infers the pathological changes of the tissue to be examined by means of the changes of the MOE value. As a brand-new imaging technology, RT-SWE can avoid many undesirable factors in the imaging process, and has the advantages of good repeatability and fast speed[16, 17]. RT-SWE makes ultrasonic elastography more perfect and has shown its effectiveness and superiority in many fields. Therefore, this study applied it to the detection of curative effects and prognosis of patients with ESRD. In this research, we first examined CKD patients with and without ESRD using RT-SWE. By comparing the difference of MOE values between the two cohorts, we found that patients with ESRD presented higher MOE values than those without. It has been mentioned in some studies that with

the gradual progression of the disease, the kidneys of patients with CKD will also develop some histological changes, such as progressive spherical atherosclerosis, vascular sclerosis and tubular injury, including tubular atrophy and interstitial fibrosis. Fibrosis reduces the elasticity of tissues, which may lead to a significant increase in MOE in patients with ESRD[18, 19]. At the same time, the difference between the two cohorts inspired us to determine whether MOE can be used to diagnose ESRD. Therefore, we drew the ROC to test the value of MOE in diagnosing ESRD in CKD patients and found that the AUC, specificity and sensitivity were 0.880, 82.09, and 84.38%, respectively, which indicated that MOE was of high diagnostic value in ESRD. In addition, in the study of Çildağ et al., it was also found that the use of RT-SWE can also assist in the completion of renal biopsy(18), which further supports the point of view of this experiment, indicating that RT-SWE is extremely effective in renal tissue performance. excellent. Not only that, RT-SWE has also been proven to have good imaging effects in diseases such as portal hypertension and breast cancer, which can assist clinical diagnosis of early disease[19, 20]. This also fully reminds us that RT-SWE may have potential diagnostic significance in many clinical diseases in the future.

For ESRD patients, hemodialysis is clinically an effective alternative to kidney function to achieve the elimination of various toxic and harmful substances produced by metabolism in the body. Dialysis can not only alleviate the clinical symptoms of patients with ESRD, but also prolong their survival time[21]. However, it is difficult for dialysis to remove some small molecules and uremic toxins completely. In addition, with the increase of treatment time, increasing toxins will be accumulated, which will cause damage to the patient's body[22, 23], so it is necessary to diagnose the curative effect of patients after treatment. We found by RT-SWE that patients with improved condition had notably lower MOE values than those with the deteriorated condition. The area under the ROC curve of MOE in the diagnosis of ESRD was 0.781, indicating that MOE may be a feasible diagnostic index of ESRD.

Finally, the analysis of the survival of ESRD patients determined lower 3- and 5-year survival in patients with high MOE values compared with those with low MOE values. And the ROC curve showed that the AUC, specificity and sensitivity of MOE for predicting 3-year survival were 0.780, 68.33, and 90.91%, while those for predicting 5-year survival were 0.856, 68.00, and 83.33%, respectively. Nevertheless, the RT-SWE technology also has some disadvantages. In view of the fact that the detection mechanism is related to the force and elasticity of the patient's tissue, we need to be careful not to exert external pressure on the test tissue, otherwise, it may affect the test results; Besides, patients need to control their breath during detection.

This study also shows some room for improvement. First, healthy controls are not included in this study for comparison. Second, since some adverse reactions in the treatment process of patients have not been studied in-depth, further investigation is warranted to determine the relationship between these adverse reactions and the research results. In summary, RT-SWE is of evaluation and prediction value for the treatment effect and prognosis of patients with ESRD, which may be a potential application index.

References

1) Adira Levin A, Piccoli G B, Alrukhaimi M, et al. What We Do and Do Not Know About Women and Kidney Diseases; Questions Unanswered and Answers Unquestioned: Reflection on World Kidney Day and International Woman's Day. J Urol Ren Dis 2017; 10: 2575-7903.

2) Parent-Roberge H, Deshayes TA, Fortier C, Marquis K, Lacharité-Lemieux C, Rodrigue C, Dionne IJ, Agharazii M, Godin M, Riesco E. Feasibility of an Intradialytic Combined Exercise Program Targeting Older Adults With End-Stage Renal Disease. J Aging Phys Act 2021; 1-10.

3) Promny D, Hauck T, Cai A, Arkudas A, Heller K, Wullich B, Apel H, Horch RE, Ludolph I. Abdominal Panniculectomy Can Simplify Kidney Transplantation in Obese Patients. Urol Int 2021; 1-8.

4) de Jong RW, Stel VS, Heaf JG, Murphy M, Massy ZA, Jager KJ. Non-medical barriers reported by nephrologists when providing renal replacement therapy or comprehensive conservative management to end-stage kidney disease patients: a systematic review. Nephrol Dial Transplant 2021; 36: 848-862.

5) Wang X, Hong J, Zhang T, Xu D. Changes in left ventricular and atrial mechanics and function after dialysis in patients with end-stage renal disease. Quant Imaging Med Surg 2021; 11: 1899-1908.

6) Qian X, Li R, Lu G, Jiang L, Kang H, Shung KK, Humayun MS, Zhou Q. Ultrasonic elastography to assess biomechanical properties of the optic nerve head and peripapillary sclera of the eye. Ultrasonics 2021; 110: 106263.

7) Wang P, Wu P, Jia B, Liang J, Han Z, Xie F. Analysis of the predictive value of real-time shear wave elastography in detecting the elastic hardness of liver and spleen in patients with portal hypertension of hepatitis B cirrhosis. Panminerva Med 2021.
8) Li SM, Wang YA, Liu W, Wu ZY, Chen L, Cai XL, Zhang R, Yang WJ, Liu Y, Ma YM, Gong SQ. Urinary retinol-binding protein and β-microglobulin were associated with urinary albumin to creatinine ratio and renal function in hospitalized diabetic patients). Zhonghua Nei Ke Za Zhi 2021; 60: 438-445.
9) Gutierrez-Peña M, Zuñiga-Macias L, Marin-Garcia R, Ovalle-Robles I, García-Díaz AL, Macías-Guzmán MJ, Delgado-Bentites A, Macías-Diaz DM, Prado-Aguilar CA, Vega de la Rosa A, Delgadillo-Castañeda R. High prevalence of end-stage renal disease of unknown origin in Aguascalientes Mexico: role of the registry of chronic kidney disease and renal biopsy in its approach and future directions. Clin Kidney J 2021; 14: 1197-1206.
10) Kittiskulnam P, Tiskajornsiri K, Katavetin P, Chaiwatanarat T, Eiam-Ong S, Praditpornsilpa K. The failure of glomerular filtration rate estimating equations among obese population. PLoS One 2020; 15: e0242447.
11) Bonani M, Seeger H, Weber N, Lorenzen JM, Wüthrich RP, Kistler AD. Safety of Kidney Biopsy when Performed as an Outpatient Procedure.Kidney Blood Press Res 2021; 1-13.
12) Nielly H, Mathian A, Cazenave M, Izzedine H, Haroche J, Cohen-Aubart F, Hie M, Miyara M, Pineton de Chambrun M, Benameur N, Hausfater P. Safety and effectiveness of transjugular renal biopsy for systemic lupus erythematosus and antiphospholipid antibody syndrome patients taking antithrombotics. Nephrol Dial Transplant; 2020; 35: 1721-1729.
13) Thanaboonnipat C, Sutayatram S, Buranakarl C, Choisunirachon N. Renal ultrasonographic shear-wave elastography and urinary procollagen type III amino-terminal propeptide in chronic kidney disease dogs. Vet World 2020; 13: 1955-1965.
14) Japanese Society of Nephrology, Essential points from Evidence-based Clinical Practice Guidelines for Chronic Kidney Disease 2018. Clin Exp Nephrol 2019; 23: 1-15.
15) Ronco C. The rise of expanded hemodialysis. Blood Purification 2017; 44(2): I-VIII.
16) Zjacic Puljiz D, Mestrovic A, Zaja I, Tonkin A, Grgurevic I, Duplancic D, Delic Jukic IK, Ljutic D, Puljiz Z. Impact of hemodialysis on liver stiffness measured with real-time two-dimensional shear wave elastography. Wien Klin Wochenschr 2021; 133: 96-101.
17) Liu Q, Wang Z. Diagnostic value of real-time shear wave elastography in children with chronic kidney disease. Clin Hemorheol Microcirc 2021; 77: 287-293.
18) Çildağ MB, Gök M, Abdullayev O. Pre-procedural shear wave elastography on prediction of hemorrhage after percutaneous real-time ultrasound-guided renal biopsy. Radiol Med 2020; 125(8): 784-789.
19) Wang JW, Guo ZX, Lin QG, Zheng W, Zhuang SL, Lin SY, Li AH, Pei XQ. Ultrasound elastography as an imaging biomarker for detection of early tumor response to chemotherapy in a murine breast cancer model: a feasibility study. Br J Radiol 2018; 91(1085): 20170698.
20) Prophet B, Berzigotti A, Abraldes JG, Turon F, Hernandez-Gea V, García-Pagán JC, Bosch J. Real-time shear-wave elastography: applicability, reliability and accuracy for clinically significant portal hypertension. J Hepatol 2015; 62(5): 1068-1075
21) Chandrasekaran V, Carta G, da Costa Pereira D, Gupta R, Murphy C, Feifel E, Kern G, Lechner J, Cavallo AL, Gupta S, Casement F. Generation and characterization of iPSC-derived renal proximal tubule-like cells with extended stability. Sci Rep 2021; 11: 11575.
22) Nowak N, Yamanouchi M, Satake E. The Nephroprotective Properties of Extracellular Vesicles in Experimental Models of Chronic Kidney Disease: A Systematic Review. Stem Cell Rev Rep 2021: 1-31.
23) Chen L, Chen G, Kong X. Serum level of high mobility group box protein-1 and prognosis of patients with end-stage renal disease on hemodialysis and peritoneal dialysis. Medicine 2021; 100(5): e24275.
24) Donati G, Cappuccilli M, Donadei C, Righini M, Scrivo A, Gasperoni L, Zappulo F, La Manna G. Toxin Removal and Inflammatory State Modulation during Online Hemodiafiltration Using Two Different Dialyzers (TRIAD2 Study).Methods Protoc 2021; 4(2): 26.
25) van Gelder MK, Middel IR, Vernooij RW, Bots ML, Verhaar MC, Masereeuw R, Grooteman MP, Nubé MJ, van den Dorpel MA, Blankestijn PJ, Rookmaaker MB. Protein-Bound Uremic Toxins in Hemodialysis Patients Relate to Residual Kidney Function, Are Not Influenced by Convective Transport, and Do Not Relate to Outcome. Toxins 2020; 12(234): 234.

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