

The Idea of Establishing the Animal Model of Qi Deficiency and Blood Stasis in Chronic Renal Failure from the Perspective of Combining Disease and Syndrome Based on the Quantitative Model

Zhao Renwei^{1,a}, Zhang Wanfang^{1,b}, Wang Yuetong^{2,c}, Yin Jiyao^{1,d}, Shen Xia^{1,e}, Yu Lili^{3,f},
Wang Junwen^{4,g}, Qu Kai^{1,5,h,*}

¹Shaanxi University of Chinese Medicine, Xi'anyang, Shaanxi, 712046, China

²Shaanxi Academy of Traditional Chinese Medicine, Xi'an, Shaanxi, 710003, China

³Macau University of Science and Technology, Macau, 999078, China

⁴China Academy of Chinese Medical Sciences, Beijing, 100105, China

⁵Shaanxi Provincial Hospital of Chinese Medicine, Xi'an, Shaanxi, 710003, China

^azhaorenwei1@163.com, ^b601668368@qq.com, ^cwytdeemailo@163.com,

^dyy13505219957@163.com, ^ejxrain@163.com, ^fiamaishui@163.com, ^gwangjww@hotmail.com,

^h18792508567@163.com

*Corresponding author

Keywords: Chronic renal failure; Combination of disease and syndrome; Animal model; Qi deficiency and blood stasis syndrome

Abstract: Based on the animal model of chronic renal failure at the present stage, we used the clinical identification method of integrated Chinese and western medicine, to explore the idea of constructing the syndrome model of Qi deficiency and blood stasis under the mode of combining disease and syndrome. The establishment and evaluation methods of animal models of chronic renal failure in recent years were summarized, and the advantages and disadvantages of different models were compared and analyzed. The establishment methods, anastomosis, reliability and practicability of the model combining disease and syndrome were explored in connection with the clinical symptoms of traditional Chinese and western medicine. Resultly, it was found that the animal model of disease and syndrome combination established at the present stage was only the simple addition of Western medicine disease name and TCM syndrome type, which could not completely simulate the occurrence, development and outcome of TCM syndrome.

1. Introduction

Chronic renal failure (CRF) is a type of clinical syndrome in which kidney function continues to decline until complete destruction based on the combined progression of multiple Chronic kidney diseases (CKD) [1]. The treatment of chronic renal failure with integrated Chinese and western medicine can effectively delay the progression to End stage renal disease (ESRD), as shown in Table 1 and Table 2. In order to further improve the clinical effect, Chinese and western medicine scholars

devoted themselves to the experimental mechanism research of chronic renal failure, established the animal model of chronic renal failure, and made some achievements. However, most of the established animal models are mainly physical or chemical induced models, and the established models lack the expression of TCM syndromes. The research group found in previous studies that the TCM syndrome of chronic renal failure is mainly Qi deficiency and blood stasis. Based on previous research results, this paper intends to review the current animal model of chronic renal failure from the literature, and further propose the research idea of establishing the animal model of chronic renal failure with Qi deficiency and blood stasis from the perspective of combining disease and syndrome, laying the foundation for basic research.

Table 1: Staging of chronic kidney diseases (CKD)

Staging of CKD	Glomerular filtration rate (GFR)	Kidney damage
	ml/(min.1.73 m ²)	
CKD1	≥90	GFR is normal, but clinical manifestations of kidney damage may occur
CKD2	60-90	Mild chronic renal dysfunction
CKD3	30-59	Moderate chronic renal dysfunction
CKD4	15-29	Severe chronic renal dysfunction
CKD5	<15	End stage renal disease (ESRD)

Table 2: Staging of chronic renal failure (CRF)

Staging of CRF	Serum creatinine (Scr)	Glomerular filtration rate (GFR)
	(μmol/L)	ml/(min.1.73 m ²)
Chronic renal insufficiency in compensation phase	133-177	50-80
Chronic renal insufficiency in the phase of decompensation	186-442	20-49
Chronic renal failure in renal failure phase	451-707	10-19
Uremia phase	≥707	<10

2. Analysis of the establishment status of animal models of chronic renal failure reported in the literature

At present, the animal models of chronic renal failure are mainly induced by physical, chemical or both methods, and the physical factors are mainly the irreversible damage of kidney tissue caused by surgical intervention. Chemical factors mainly use the nephrotoxicity of drugs or biological serum to cause irreversible damage to nephron [2]. The way of combining the two is mainly to first use a physical or chemical way to deal with it, and then use another method to mold it, so as to achieve irreversible damage to the kidney [3]. According to the needs of the experiment, mice and rats are often used for modeling animals. However, due to the small size of mice, the drug quantity control is prone to deviation and it is difficult to obtain materials, which affects the experimental results and data observation. The size of rats is moderate, the anatomical shape of the kidneys is similar to that of humans, and the resistance to disease and infection is strong, so rats are mostly selected for modeling in the experiment.

At present, the commonly used chemical modeling methods are: (1) doxorubicin induced model [4]: Rat tail intravenous injection of 4mg kg⁻¹ 7d⁻¹ for two weeks can induce typical focal segmental

glomerulosclerosis and chronic renal failure. As one of the classical models for the study of chronic renal failure, this model has the advantages of simple operation, low mortality and high model stability, but due to strong toxicity, it is easy to produce toxic effects on the heart and digestive tract and reduce the model formation rate. (2) Animal model of adenine: Xu et al. [5] administered adenine at 250mg kg⁻¹ d⁻¹ to rats by gavage, which produced a large amount of proteinuria at 28 days, and significantly increased urea nitrogen and serum creatinine. The model has the advantages of simple operation, short modeling cycle and high molding rate, but it also has the disadvantages of high mortality and large individual differences. (3) Animal model of aristolochic acid: Zhu et al. [6] administered aristolochic acid at 5mg kg⁻¹ d⁻¹ to rats by intragastric administration, which lasted for 12 weeks and showed obvious renal tubule atrophy, increased renal interstitial area, decreased renal tubule area, and multifocal fibrosis of renal interstitial cells. The model is simple to operate and has little trauma, but the molding cycle is too long and the molding effect is unstable. (4) Xenogenic serum induction model: Hsu et al. [7] first pre-immunized rats with cationic bovine serum albumin (C-BSA) 0.5mg and Escherichia coli endotoxin 0.25μg by injecting them with tail vein 1 week later 12mg d⁻¹ for 5 weeks, and then 12mg 2d⁻¹ for 5 weeks, for a total of 11 weeks. The model is simple to operate and can simulate the natural onset, course and outcome of human chronic renal failure. However, the modeling time is longer, the mortality rate is higher, the modeling rate is lower, and the repeatability is poor.

Compared with chemical modeling methods, the commonly used physical modeling methods are: (1) Animal models of large part nephrectomy: Dong et al. [8] prepared a rat animal model of chronic renal failure by 5/6 nephrectomy. The method was mainly divided into two steps: 5/6 of the rat renal tissue was removed successively, so that the residual kidney could gradually cause the loss of renal function and the formation of renal fibrosis under the conditions of high pressure, high perfusion and high filtration. Because it is a surgical operation, the operator has certain technical requirements, the operation is complicated, easy to cause bleeding, infection, and even death of animals, because of its long molding cycle, so it is limited in the experiment; (2) ischemia-reperfusion model: Chen et al. [9] surgically removed the right kidney, clipped the left renal pedicle with an undamaged artery clamp, opened the artery clamp 50 minutes later to restore blood supply, and observed the model 10 weeks later. This model has strong significance for chronic renal failure caused by kidney transplantation. The disadvantages are that it has certain technical requirements for operators, and the modeling cycle is long, which is easy to cause infection and death in animal models. (3) Animal model of unilateral ureteral ligation: Tian et al. [10] used unilateral ureteral ligation to induce a mouse model, resulting in renal tubule atrophy, renal interstitial edema, inflammatory infiltration and a large number of fibrous tissue hyperplasia, which evolved into chronic renal failure with the progression of the disease. The model has the advantages of relatively simple operation, high molding rate, low mortality and high repeatability, but the disadvantage is that surgical operation is required, and the animal model is easy to cause bleeding infection or even death.

The composite modeling methods mainly included: unilateral nephrectomy combined with adriamycin model: Shi Lixia et al., ligation and resection of the right kidney of rats, injected adriamycin in the tail vein twice on the 7th and 14th day after surgery, a total of 8mg/kg, and finally successfully constructed the chronic renal failure model. The pathological changes of the model kidney, such as obvious swelling, inflammatory cell infiltration, large amount of protein-like substances in the lumen, punctated necrosis, were similar to those of patients with chronic renal failure in the clinic. Compared with a single method, the model construction method is complex, with short time, high modeling rate and low mortality. The disadvantage is that surgical operation is required, the operating environment and operators have certain requirements, and infection and death are easy to occur [37]. Unilateral nephrectomy combined with puromycin model modeling method: Hiong L C et al., first ligation and excision of one kidney in rats, and then injected 150 mg/kg

puromycin intraperitoneally, successfully established the model. This model has a simple construction method, which is suitable for the study of pathological damage, pathogenesis and drug intervention in micropathological nephropathy and focal segmental glomerulosclerosis. The disadvantage is that such models are rarely used, and their stability and popularization need to be further verified [38].

The current chemical, physical and combined modeling methods can simulate the pathological changes of glomerulosclerosis and renal interstitial fibrosis, reflecting the expression of clinical symptoms to a certain extent, but for the expression of TCM syndromes, the relevant models have not been drawn. Therefore, how to establish an animal model of chronic renal failure conforming to the evolution law of TCM syndromes is the premise of objectifying the syndromes.

3. Establish the status analysis of standardization of syndrome from the perspective of combination of disease and syndrome

The combination of disease and syndrome refers to the research on TCM syndromes under the conditions clearly defined by modern medicine, that is, selecting clinical diseases with clear Western medicine diagnosis and advantages in TCM treatment, systematically observing and discussing the pathogenesis and evolution of TCM in different Western diseases, and establishing a targeted system of combining disease and syndrome with syndrome and syndrome is an important way to standardize the syndromes [11]. The difficulty of standardizing syndromes lies mainly in the fact that syndromes are multi-dimensional and multi-stage, systematic and complete, including etiology, disease, disease location, disease potential, etc. Without any part of content, clinical guidance cannot be complete and accurate [12]. Wang [13] proposed to reduce the dimension and elevate the order of the syndrome, transforming from nonlinear to linear, seeking simple and clear expression. At the same time, Zhu et al. [14] put forward the concept of syndrome elements, believing that the diagnosis of syndrome lacks precise indicators, and all pathological information presented by patients should be analyzed as an organic whole, so as to clarify the overall state of each stage of disease development in diagnosis and treatment, and comprehensively evaluate the qualitative and quantitative relationship between symptoms and syndrome types. In order to achieve the purpose of diagnosis and differentiation, TCM needs to formulate syndrome differentiation standards applicable to the whole disease area and conduct a comprehensive analysis of the syndromes [15]. Based on the above studies, it initially reflects that there is a consensus that the study of syndromes should be objectified from the perspective of combining disease and syndrome. Therefore, the research group intends to carry out relevant research on the construction of animal models from the perspective of combination of disease and syndrome, based on the identification of syndrome elements.

4. The idea of establishing an animal model of chronic renal failure from the perspective of combining disease and syndrome

In recent years, Chinese medicine scholars, guided by the basic theory of Chinese medicine, have carried out in-depth research on the combination of disease and syndrome with animal models using various methods and different ideas and approaches. At present, the animal model of combining chronic kidney failure with disease and syndrome is mainly divided into three ways: pre-disease and post-syndrome [16] and combination of disease and syndrome [17]. Disease before syndrome is to make a disease or pathological model of Western medicine using physical or chemical factors first, and then intervene with single or multiple factors to form a unique syndrome of Chinese medicine. This is the modeling method adopted by most scholars at present, such as: Xie [16] successfully prepared the model of chronic kidney failure by doxorubicin tail vein injection, then intervened with senna leaf gavage and swimming to successfully prepare the model of spleen-yang deficiency. The

combination of disease and syndrome refers to the use of "disease" and "syndrome" modeling intervention means to act on animals together, or under the intervention of "disease" modeling means, so that both Western diseases or pathological changes and TCM syndromes can be prepared at the same time during modeling. For example, Hong et al. [17] used adenine for the preparation of animal models, and rats showed obvious symptoms of kidney-yang deficiency 21 days after the preparation of the models.

The above studies have revealed the expression of TCM syndromes in Western medical diseases, but the syndromes are a multi-dimensional and multi-order nonlinear complex system [18], and how to deepen the understanding of syndromes is an urgent problem to be solved at present. Wang et al. [19] believe that syndrome is the overall reaction state of human physiology and pathology, which is characterized by internal and external deficiency, dynamic space-time and multidimensional interface. The internal reality here refers to the physical zang-fu organs on which TCM Tibetan images rely, while the external vacuity refers to the various life information displayed by the human body in the outside world, which form dynamic comprehensive effects with the change of time and space, so it can also be considered as a living organism composed of a multidimensional interface that moves in time [20]. Wang et al. [21] further summarized the syndromes and found that although the syndromes are mainly composed of two major factors reflecting the location and nature of the disease, there are still certain ambiguities in TCM syndrome differentiation in clinical diagnosis and treatment due to the different diagnosis and treatment experience of doctors, the different complexity of the disease, the combination of multiple syndrome differentiation methods and the non-standard use of syndrome names. As Zhu's [14] study pointed out, the diagnosis of syndrome lacks precise indicators, and all pathological information should be analyzed as an organic whole to diagnose the overall state of the body at the present stage of the disease from all aspects to comprehensively evaluate the qualitative and quantitative relationship between symptoms and syndrome types. Therefore, how to quantify syndromes and introduce them into animal models is the difficulty of current research.

5. Renal pathology was introduced from the perspective of macro and micro syndrome differentiation as an extension of the four diagnoses

Compared with the understanding of diseases in traditional Chinese medicine, Western medicine pays more attention to the understanding and diagnosis of etiology and pathology, especially the occurrence and development of diseases in the microscopic state, so it is easier to form consistent diagnostic criteria. The formation of TCM "syndrome" is not only affected by specific factors, but also involves weather, environment, diet and other factors, so the "syndrome" formed is complicated. Combining the micro-diagnosis of Western medicine with the macro-diagnosis of Chinese medicine (holistic view and dynamic view) can effectively enhance the depth and breadth of clinical diagnosis [22]. Cheng [23] further classified the pathological products such as cell proliferation, renal interstitial fibrosis and glomerulosclerosis into the category of "solid evil" (rheumatism, cold dampness, phlegm stasis, turbidity toxicity) in the process of microscopic differentiation of kidney pathology (that is, the process of understanding the pathological changes of kidney with the theory of traditional Chinese medicine). Taking IgA nephropathy [23] and membranous nephropathy [24] as examples, studies on the correlation between syndrome and kidney pathology were carried out. For example, in IgA nephropathy studies, patients showed frequent nocturnal urination, fatigue, renal anemia and other diseases, and the macroscopic syndrome differentiation was spleen and kidney qi deficiency syndrome. Pathological examination showed renal tubule atrophy, renal interstitial fibrosis, and its internal morphological changes. The microscopic syndrome was phlegm and blood stasis interjunction syndrome. The combination of microscopic syndrome and macroscopic syndrome was in line with the understanding of the pathogenesis of traditional Chinese medicine. Qu [36] analyzed

the renal pathology and syndrome distribution of IgAN and found that the distribution of IgAN syndrome was related to renal pathological types, immune deposits and Katafuchi score to a certain extent. For example, there were more types of immune deposits in deficiency syndrome. In the Katafuchi integral, the degree of damage to renal interstitial tubules, glomerulus and blood vessels in renal tissue was quantified integrally. The deficiency syndrome was dominant when there was no crescent body, while heat toxicity, blood stasis, dampness and heat were more common after the crescent body appeared, which was consistent with LEE's grading. It is proved that it is feasible to carry out the standardization research of syndrome from the perspective of macro syndrome differentiation and micro syndrome differentiation.

6. The idea of establishing the animal model of qi deficiency and blood stasis in chronic renal failure from the perspective of combining disease and syndrome based on the quantitative model

Syndrome differentiation has multi-dimensional complexity, and each symptom has different contribution degree to the judgment of each syndrome element. Our research group [25-28] has carried out research on the quantitative expression of chronic renal failure syndromes. For example, Wang et al. [29-33] studied chronic kidney failure, chronic obstructive pulmonary disease and viral hepatitis B, carried out literature and clinical research on syndromes from the perspective of combining disease and syndrome, and objectified the expression of syndromes through syndrome differentiation scale and various mathematical statistics methods. Qu et al. carried out a study on syndrome factor differentiation scale around chronic renal failure and explained the scores of different syndrome elements. If the corresponding symptoms of qi deficiency are low qi and lazy talk (10 points), fatigue (10 points), spontaneous sweating (9 points), weak tongue (8 points), easy to catch cold (8 points), etc. , the syndrome element score ≥ 10 points, that is, the diagnosis of the syndrome element is established. The method of integral quantification is used to evaluate the factors of syndrome, which has certain characteristics such as scientificity, practicability, development, inheritance, stability and differentiation [34].

Applying quantitative thinking to the verification of the animal model of the combination of disease and syndrome makes the evaluation of the combination of disease and syndrome objective, and gradually transforms from qualitative to quantitative, which has far-reaching significance for exploring the coincidence rate of the syndrome expression of the model. After years of experimental observation, Zhang et al. [39] developed a quantification table for the blood stasis syndrome model of rats, including tongue quality, sublingual veins, eye color and tail ecchymosis, which was divided into three grades of light, medium and heavy, and its quantification model was unanimously recognized by domestic scholars. Yuan [40] improved Li's [41] Qi-deficiency syndrome differentiation scale (mental status, hair, stool traits) on the basis of the research, added the color of the ear tail, and carried out semi-quantitative quantification of four items, such as the color of the ear tail: Pale or clear cyan (3 points), light white Shaoze (2 points), light red Shaoze (1 point), red luster (0 points), the four items of the model were quantified respectively, and the score was ≥ 4 points, that is, the syndrome type was established.

In the research group's previous studies on chronic renal failure, it was found that the main TCM syndromes were Qi deficiency and blood stasis. TCM believed that qi promoted blood to run the whole body, and if there was improper diet, overwork and chronic physical deficiency, it would lead to the depletion of qi and blood, resulting in the weakness of Qi to promote blood operation and the formation of blood stasis. The generation of blood stasis will also block the operation of Qi, further damage qi and blood, "deficiency" and "blood stasis" affect each other, resulting in the emergence of Qi deficiency and blood stasis. Based on the etiology and pathogenesis of clinically common Qi-

deficiency and blood-stasis syndrome of chronic renal failure, the research group plans to use physical or chemical means to create a model while conducting etiology intervention of chronic renal failure in animals, so as to make its pathogenesis and development outcome as similar as possible to clinical practice. After successful model intervention, microscopic examination of renal pathology will be conducted to form microscopic diagnosis. Such as glomerular sclerosis, renal interstitial fibrosis, crescent body formation and immune complex deposition (IgA, IgM, IgG, C3, FRA, etc.) deposition changes. Semi-quantitative integral evaluation was carried out on their symptoms to clarify the macro diagnosis of TCM syndroms, such as mental malaise in rats and disappearance of aggression or antagonism (Qi-deficiency score 3 points); Loose skin, withered hair, falling off (Qi deficiency score 3 points); Thin stool (Qi deficiency score 3 points); The color of ear and tail was pale or cyan, and there were moderate petechiae in the tail (Qi-deficiency score 3 points, blood stasis syndrome score 3 points); Purple tongue or ecchymosis petechiae (blood stasis syndrome score 3 points). The overall Qi-deficiency score of the model is > 4 points, and the score of blood stasis syndrome is > 4 points, that is, the model is considered to be in line with the Qi-deficiency and blood-stasis syndrome of traditional Chinese medicine syndrome. In the follow-up treatment and intervention, the targeted treatment of supplementing Qi and promoting blood circulation is carried out. If the effect is significant, the model is considered to be in line with the Qi-deficiency and blood-stasis syndrome of chronic renal failure. The emergence of this quantitative model, discarding the past local pathological changes or subjective judgment as the diagnostic basis, the performance of animal models are digitized and objectified, providing scientific support for the construction of disease and syndrome combination model.

7. Conclusion

The combination model of disease and syndrome is the main trend of animal models of traditional Chinese medicine. It integrates TCM syndrome factors with modern medical animal models, which can well reflect the understanding of traditional Chinese medicine and western medicine on the etiology, pathogenesis, development law and prevention and treatment measures of diseases, accurately express the periodic and dynamic changes of TCM syndromes, and at the same time has the characteristics of high credibility, strong objectivity and in line with the law of disease evolution. Starting from the etiology and pathogenesis of chronic renal failure, based on the development and outcome of the disease, the author combined "disease" and "syndrome" organically by means of complex model, clarified the microscopic syndrome differentiation through pathological detection, systematically evaluated the syndrome of the model through semi-quantitative integral scale, clarified the macroscopic syndrome differentiation, and then tested the consistency of the constructed animal model through "testing the syndrome by means of prescription". To exclude the model of the combination of false disease and syndrome. The model established by this method can not only effectively express the disease or pathological changes of Western medicine, but also reflect the guidance of basic theories of Chinese medicine and scientific testing methods. At the same time, the establishment of the model of the combination of disease and syndrome is the basis of promoting the modernization of traditional Chinese medicine, and has far-reaching significance for the research of disease and the development of clinical new drugs.

References

- [1] Chen Xiangmei, Ni Zhaohui, Liu Yuning, et al. *Diagnosis and treatment guide of integrated Chinese and Western medicine for chronic renal failure [J]. Hebei Chinese Medicine, 2016, 38 (02):313-317.*
- [2] Lin Jiuru, Gou Fangfang, Li Xueming, et al. *Establishing an animal model of chronic renal failure in rats with glomerular and tubulointerstitial injury [J]. Chongqing Medical Journal, 2016, 45 (14):1882-1885.*
- [3] Hu Ankang, Zhu Xiaorong, Yuan Honghua. *Establishment of a rat model of chronic renal failure [J]. Chinese Journal*

of *Experimental Animal*, 2011, 19 (01):34-38+94.

[4] Xiong T, Attar M, Gnirck A C, et al. Interleukin-9 protects from early podocyte injury and progressive glomerulosclerosis in Adriamycin-induced nephropathy [J]. *Kidney International*, 2020, 98(3):615-629.

[5] Xu Ke, Huang Xuekuan, Shen Qing, et al. Effects of *Panax notoginseng* Saponins on the AngII/AT1R/ERK1/2 Signaling Pathway of Rats with Chronic Renal Failure [J]. *Traditional Chinese Drug Research and Clinical Pharmacology*, 2021, 32(10):1417-1424.

[6] Zhu Bingbing, Yao Weiguo, Wang Hao, et al. The mechanism of chronic hypoxic injury in aristolochic acid nephropathy and the intervention effect of Wenyang Huoxue formula [J]. *Chinese Journal of Clinical Pharmacology*, 2018, 34(16):1978-1981.

[7] Xu Yachao, Qiu Liying, Xu Huan, et al. Comparison of three kinds of modeling methods in chronic renal failure rats [J]. *Jiangxi Traditional Chinese Medicine*, 2016, 47(02):57-59.

[8] Dong Xiang, Hu Shuang, Wang Qian, et al. Effect of Liuwei Dihuang Decoction on hypoxic-induced-factor-1 α and expression of Twist and E-cadherin in 5/6 nephrectomized rats [J]. *Journal of Beijing University of Chinese Medicine*, 2019, 43(11):927-934.

[9] Chen Guoxiao, Liu Xiuheng, Zhang Xiangsheng, et al. Effect of ozone oxidation on renal ischemia-reperfusion injury [J]. *Chinese Journal of Modern Medicine*, 2017, 27 (09):19-24.

[10] Tian T, Zhang J, Zhu X, et al. FTY720 ameliorates renal fibrosis by simultaneously affecting leucocyte recruitment and TGF- β signalling in fibroblasts [J]. *Clinical & Experimental Immunology*, 2017, 190(1).

[11] Wang Tianfang, Xue Xiaolin, Wang Qingguo. Current situation and prospect of scale in Chinese medicine research [J]. *Journal of Beijing University of Chinese Medicine*, 2006, 29 (5):293-295.

[12] Li Dongtao. The principle of argumentation [J]. *Journal of Sichuan of Traditional Chinese Medicine*, 2010, 28 (12):24-26.

[13] Wang Yongyan. Suggestions on improving the method system of TCM syndrome differentiation [J]. *Journal of TCM*, 2004(10):729-731.

[14] Zhu Wenfeng. Study on syndrome element differentiation [J]. *Henan Chinese Medicine*, 2009, 29 (01):1-4.

[15] Zhu Yinghua, Deng Ali, Deng Chun, et al. Quantitative diagnosis of spleen deficiency phlegm-dampness syndrome of polycystic ovary syndrome [J]. *Chinese Journal of Traditional Chinese Medicine*, 2019, 61(12):1080-1084.

[16] Xie Chen, Xu Peng, Liang Xing, et al. Changes of expression of renal aquaporins in the model of spleen Yang deficiency syndrome combined with nephrotic syndrome [J]. *Chinese Journal of Traditional Chinese Medicine*, 2018, 33(03):929-933.

[17] Hong Chunlan, Li Zheming, Li Changyu. Effect of Zhenwu Decoction on renal protection in rats with kidney-yang deficiency chronic renal failure [J]. *Journal of Zhejiang Chinese Medicine University*, 2015, 39 (01):57-61.

[18] Zhang Zhibin, Wang Yongyan, Lv Aiping, et al. On Combined Syndrome Differentiation of Essential Elements of Syndrome and Syndrome Target Point Corresponding Syndromes [J]. *Journal of Traditional Chinese Medicine*, 2006, 47(7):483-485.

[19] Wang Yongyan. Suggestions on improving the method system of TCM syndrome differentiation [J]. *Journal of TCM*, 2004(10):729-731.

[20] Guo Xiachen. Thoughts on the study of Traditional Chinese Medicine Tibetan-image theory [J]. *Journal of Beijing University of Traditional Chinese Medicine*, 2008(08):512-514.

[21] Wang Tianfang. Establishment of diagnostic criteria for combination of disease and syndrome [J]. *Chinese Journal of Integrated Traditional and Western Medicine*, 2011, 31 (08):1025-1026.

[22] Wang Tianfang. Establishment of diagnostic criteria for combination of disease and syndrome [C]// *Chinese Journal of Integrated Traditional and Western Medicine*, 2012:309-310.

[23] Cheng Xiaohong, Yu Xiaoyong, Mao Jiarong. Pathological changes of IgA nephropathy and microscopic differentiation of traditional Chinese medicine [J]. *Chinese Journal of Integrated Traditional and Western Nephrology*, 2014, 15(02):185-186.

[24] Zhang Xiaofeng, Cheng Xiaohong, Tian Yun, et al. Study on correlation between TCM syndrome distribution and clinicopathological stage of idiopathic membranous nephropathy [J]. *Shaanxi Traditional Chinese Medicine*, 2017, 38(08):1051-1053.

[25] Qu Kai, Wang Tianfang, Zhao Yan, et al. Expert questionnaire survey on four diagnostic information related to chronic renal failure syndrome elements [J]. *Journal of Shandong University of Traditional Chinese Medicine*, 2011, 35 (03):274-277.

[26] Qu Kai. Study on the contribution degree of chronic renal failure related symptoms to syndrome factors based on expert consultation questionnaire [J]. *China Medical Review*, 2015, 12 (27):52-54+70.

[27] Qu Kai, Wang Tianfang, Zhao Yan, et al. Research on common TCM syndromes of chronic renal failure based on expert consultation questionnaire [J]. *Journal of Integrative Chinese and Western Medicine*, 2010, 8 (12):1147-1152.

[28] Li Zhigeng, Wang Tianfang, Xue Xiaolin, et al. Development and evaluation of symptom information collection table of chronic renal failure for syndrome research [J]. *Journal of Beijing University of Chinese Medicine*, 2006(09):599-

602+606.

- [29] Wu Xiuyan, Wang Tianfang, Zhao Yan, et al. Literature study on combination of TCM syndromes of depression, chronic hepatitis B and chronic renal failure [J]. *Chinese Journal of Basic Medicine of Traditional Chinese Medicine*, 2008(10):763-764.
- [30] Wu Xiuyan, Wang Tianfang, Chen Jianxin, et al. Study on correlation between pathogenic syndrome elements and symptoms of depression, chronic hepatitis B and chronic renal failure based on correlation degree method [J]. *Tianjin Chinese Medicine*, 2009, 26 (05):433-435.
- [31] Yu Lili, Wang Tianfang, Jiao Yang, et al. Study on common TCM syndromes of chronic obstructive pulmonary disease based on expert questionnaire survey [J]. *Chinese Journal of Traditional Chinese Medicine*, 2011, 26 (07):1504-1507.
- [32] Yu Lili, Wang Tianfang, et al. Clinical study on syndrome and distribution characteristics of syndrome elements in stable chronic obstructive pulmonary disease [J]. *Journal of Beijing University of Chinese Medicine*, 2010, 33 (10):699-702.
- [33] Xu Wenjie, Wang Tianfang, Wang Zhiyu, et al. Study on common symptoms of chronic obstructive pulmonary disease in stable period based on hidden structure method [J]. *Journal of Beijing University of Chinese Medicine*, 2011, 34 (02):82-86.
- [34] Qu Kai. Establishing diagnostic criteria for chronic renal failure based on syndrome elements and combination model [J]. *Chinese Journal of Traditional Chinese Medicine*, 2014, 29 (11):3364-3365.
- [35] Li Nan, Liu Li. Professor Liu Li summarizes the modeling method of Qi-stagnation and blood-stasis salpingitis [J]. *World Journal of Integrated Chinese and Western Medicine*, 2019, 14(05):626-629.
- [36] Qu Kai, Yu Xiaoyong, Cheng Xiaohong, et al. Analysis of correlation between syndrome distribution and renal pathology in IgA nephropathy [J]. *Shaanxi Traditional Chinese Medicine*, 2014, 35(08):957-960.
- [37] Shi Lixia, Liu Xiaomin, ZHANG Zhenjia, et al. Effect of Shenshuaikang Oral Liquid on renal failure in chronic renal failure rat model [J]. *Chinese Journal of Gerontology*, 2016, 36(12):2863-2864.
- [38] Hiong LC, Voon KL, Abdullah NA, et al. Effect of TGF-beta1 antisense oligodeoxynucleotide on renal function in chronic renal failure rats. *Acta Pharmacol Sin.* 2008, 29(4):451-457.
- [39] Zhang Bin, Wang Zhonghua, Wang Jiangrong, et al. Establishment and evaluation of a rat model of liver fibrosis with blood stasis [J]. *Chinese Journal of Basic Medicine of Traditional Chinese Medicine*, 2006(11):836-838.
- [40] Yuan Guoqiang, Wu Shizhen, Jia Zhenhua, et al. Establishment method of animal model of excess qi deficiency syndrome [J]. *Chinese Journal of Traditional Chinese Medicine*, 2009, 24 (04):469-471.
- [41] Li Jing, Wang Jian. Evaluation of the effectiveness of supplementing Qi and activating blood in improving the biological characteristics of focal cerebral ischemia-reperfusion model rats with Qi deficiency and blood stasis syndrome [J]. *Chinese Journal of Basic Medicine of Traditional Chinese Medicine*, 2003(04):22-26.