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Determining diabetic kidney disease severity using traditional Chinese medicine syndrome classification

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INTRODUCTION

Diabetic kidney disease (DKD) is a severe and common complication of type 2 diabetes mellitus (T2DM) that is associated with high rates of morbidity and mortality. Half of the patients with T2DM could develop DKD after 25-years of disease, and a third of patients with DKD progress to end-stage renal disease (ESRD).[1] Accordingly, DKD was detected in approximately half of the patients attending outpatient diabetes care in Singapore,[2] and DKD represents the most common cause of ESRD locally.[3] Hence, it is not uncommon for patients with DKD to seek complementary alternative treatment, which many patients consider as possessing fewer side-effects compared to Western medications.

Traditional Chinese Medicine (TCM) is the most popular complementary alternative medication in Singapore, and interestingly, TCM is also commonly used by the Malay and Indian communities.[4] However, despite the acceptance of TCM treatment among the general population, patient care between conventional Western medicine trained physicians and TCM physicians are not well-integrated. Worryingly, 74% of patients do not inform their Western medicine physicians that they are concurrently receiving TCM treatment.[4] Therefore, patients with DKD will often visit their TCM physicians without adequate medical information or laboratory test results, such as the glomerular filtrate rate (GFR). The GFR is an index of kidney function and categorizes DKD into different stages of severity.[5] This classification is also known as the Chronic Kidney Disease (CKD) classification and serves as an essential marker to prognosticate and guide DKD treatment. Clinical trials using TCM herbal medication also utilize the GFR and other measures, such as the urine protein excretion for the selection and monitoring of DKD treatment.[6,7]

In the absence of GFR values, TCM physicians are dependent solely on their clinical assessment to diagnose and stage the severity of DKD. However, the method of diagnosing DKD using TCM and conventional Western medicine is very different, and it remains

unclear whether TCM syndrome classification of DKD can detect the severity of DKD based on GFR. Further, DKD is a complex multisystem disorder, and the quality of life (QoL) of DKD patients deteriorates with the worsening of the GFR.[8,9] It is also not unknown whether TCM syndrome classification of DKD would capture this vital aspect of care.

The goal of our exploratory study was to evaluate the ability of TCM syndrome classification to capture differences in GFR among patients with DKD. We further assessed whether TCM syndrome classification could detect deterioration of QOL in patients with more severe DKD.

METHODS

We recruited subjects with T2DM and age ≥ 21 years with GFR less than 90 ml/min/m^2 from the Singapore General Hospital Diabetes and Metabolism Centre (SGH DMC). Only subjects with stable renal function, defined as no change in serum creatinine by more than 2-fold in the recent 4-weeks, were recruited. Those with the following criteria were excluded: Type 1 Diabetes; dialysis or kidney transplantation; heart failure (NYHA Class III and above); acute illness; serum alanine aminotransferase or aspartate aminotransferase above 3 times upper limit of normal; pyschosis; depression; acohol abuse; untreated thyroid disease; uncontrolled hypertension; or the presence of other diseasese that may cause nephropathy. The SingHealth Centralized Institutional Review Board approved the research protocol (CIRB Reference: 2015/2004), and all subjects provided written informed consent.

Eligible subjects were first seen at the SGH DMC. Each subject had their blood taken for laboratory measurements followed by interviewer-administered questionnaires on health-related QOL. They were then scheduled to visit the Singapore Thong Chai Medical Institution (STCMI) in the next six weeks. During their visit to the STMCI, TCM physicians examined each subject individually to perform TCM syndrome classification of DKD. No

laboratory results or additional medical information were provided to the TCM physicians. Hence, they were blinded to the patient's CKD status. To reduce potential variance in DKD diagnosis, three TCM physicians from a single centre (located at a different site from the hospital) were assigned to perform TCM syndrome classification. Standardisation was further achieved through training and the use of common data collection documents.

DKD staging was made based on the subject's GFR calculated using the CKD-EPI equation.[10] Stage I CKD was defined as a GFR ≥ 90; stage II, GFR 60-90; stage III, GFR 30-59; stage IV, GFR 15-29; and stage V, GFR < 15 ml/min.[5] We further categorised patients into CKD Stage I/II, CKD Stage III, and CKD Stage IV/V. Patients in early stages of CKD were included as a reference group so that any changes in QoL parameters can be appreciated as the severity of DKD increases.

TCM syndrome classification of DKD is a diagnostic system currently used by the STCMI to manage DKD and was developed based on the China State Drug Administration Authority's Traditional Chinese Medicine New Drug Clinical Research Guidelines (2002) (中药新药临床指导原则). TCM syndrome classification involves the collection of subject's symptomatology, the examination of the radial pulse characteristic, and tongue morphology. DKD were subsequently classified into the following categories: Spleen & Kidney *Qi* Deficiency, Spleen & Kidney *Yang* Deficiency, *Qi*-*Yin* Deficiency, Liver & Kidney *Ying* Deficiency, and *Ying*-*Yang* Deficiency. Subjects with Liver Kidney *Yin* Deficiency or Spleen Kidney *Qi* Deficiency or *Qi*-*Yin* Deficiency were considered as mild DKD; subjects with Spleen Kidney *Yang* Deficiency as moderate DKD, and Yin-*Yang* Deficiency as severe DKD (Figure 1).

Health-related QoL was determined using the RAND-36 survey instrument.[11] The RAND-36 measures perceived health in eight areas: physical functioning, pain, role limitations due to physical problems, role limitations due to emotional problems, emotional

well-being, social functioning, energy/fatigue, and general health. Scores range from 0-100, and higher scores reflect better health perception.

Categorical variables were presented as proportions, while continuous variables were reported as mean ± SD. The difference in GFR between subjects with nil, mild, moderate, and severe DKD based on TCM syndrome classification was tested using the one-way analysis of variance (ANOVA). Similarly, the difference in QoL scores between subjects in different DKD severity categories was also tested using ANOVA. All analyses were performed using SPSS version 22 (SPSS Inc., Chicago, IL, USA) and Prism 8 (GrapPad Software Inc, USA). $p < 0.05$ was considered significant.

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RESULTS

We recruited 200 subjects with DKD, and their baseline characteristics are summarized in (Supplementary Table 1). Subjects were obese with an ethnic distribution representative of the wider Singaporean society. The average duration of diabetes was 16.2 ± 8.3 years, and diabetes control was suboptimal, as evidenced by an average HbA1C of 8.3 ± 1.8 %. The majority of the subjects were treated with lipid-lowering and blood pressure-lowering medications, and 89.5% of these subjects were on angiotensin-converting enzyme inhibitors (ACEis) or angiotensin II receptor blockers (ARBs). 54.8% of the subjects had previously consulted a TCM physician for their illness (35% for DKD, and 65% for mainly muscular-skeletal illness), and when divided according to ethnic groups, 62.3% Chinese, 29.2% Malay, and 33.3% of Indian subjects reported previous TCM physician consultations.

17.4% of the subjects were grouped into CKD Stage I/II, 46% into CKD Stage III, and 36.5% CKD Stage IV/V. Average GFR for patients with CKD Stage I/II = 71.7 ± 12.1,

CKD stage III = 43.4 ± 8.4, and CKD Stage IV/V = 19.9 ± 6.2 ml/min/m^2 (Figure 2a). Twenty subjects defaulted their TCM physician visits and did not receive TCM syndrome classification. TCM syndrome classification categorized 76.7% of these subjects as having nil/mild, 13.9% as moderate, and 9.4% as severe DKD. Average GFR for subjects with nil disease = 50.2 ± 14.2, mild = 40.3 ± 19.4, moderate = 29.3 ± 19.2 and severe = 33.9 ± 19.7 ml/min/m^2. Importantly, the difference in GFR distribution between TCM syndrome groups was statistically significant ($p < 0.001$) (Figure 2b). TCM syndrome classified 87.1% of subjects with CKD Stage I/II as nil/mild disease, and 85.6% of subjects with CKD Stage III as nil/mild disease. However, only 39.4% subjects with CKD stage IV/V were categorized as moderate or severe DKD.

QoL scores tended to decrease with more severe CKD stages, but the physical function score was the only QoL domain that was significantly different between CKD groups (Supplementary Figures 1a-h). By contrast, QoL scores were lower in subjects with more severe DKD categorised using TCM syndrome classification, and significant between-group differences were detected in all eight domains of QoL (Figures 3a-h).

DISCUSSION

In this study, we examined the use of TCM syndrome classification to categorise patients to different stages of DKD severity. We found that many patients had previous visits with TCM physicians, and TCM syndrome classification can detect a significant difference in GFR. We also found that TCM syndrome classification performed better than CKD staging in discriminating differences in QoL scores.

DKD is a common and severe complication of Type 2 Diabetes. Conventional treatment of DKD focuses on achieving near-normal blood glucose, blood pressure control, and the use of agents that target the angiotensin-renin-aldosterone pathway, such as ACEis or

ARBs.[12] Newer glucose-lowering agents can also retard the worsening of DKD.[13,14] However, the renal function of a significant number of patients with DKD will continue to deteriorate despite standard medical therapy.[15,16] Also, ACEi and ARBs can worsen renal function and cause hyperkalaemia in patients with advance DKD. By contrast, TCM may be better tolerated compared to conventional Western medications.[17] Therefore, it comes as no surprise that many patients often consult TCM physicians for DKD management. Our study also found that more than half of patients with DKD had a prior consultation with TCM physicians, and interestingly, about 1/3 of patients of Indian and Malay ethnicity had previously sought help from TCM physicians. This result reflects the well-integrated socio-economic fabric of the multi-cultural Singaporean society. It is also consistent with findings from earlier studies that reported the usage of TCM across all Singaporean ethnicities in the general population[4] and patients with cancer.[18]

Although TCM has long been used by the Chinese community to treat DKD,[19,20] the diagnosis of DKD based on Western medicine and TCM is very different. Western medicine relies heavily on laboratory tests to diagnose diseases and to explain many of the disease-related signs and symptoms. By Contrast, TCM Syndrome classification is an outcome of analysis by TCM practitioner using the TCM diagnostic methods of inspection, inquiry and palpation, which includes observations such as the appearance of the tongue and the strength and rhythm of the pulse.[21] A syndrome can be defined as a categorized pattern of symptoms and signs at a specific stage during the course of a disease. Little is known whether TCM syndrome classification of DKD could detect differences in renal function measured using the GFR. Our results showed that the TCM syndrome classification of DKD is capable of detecting a significant between-group difference in the GFR. However, TCM syndrome classification diagnosed less than half of patients CKD Stage 4/5 correctly as having moderate or severe DKD. In addition, the GFR of patients with severe DKD diagnosed using

TCM syndrome appeared higher than patients with moderate DKD, but this difference was small (3.6 ml/min/m^2). Therefore, while our findings support the ability of TCM syndrome classification to detect DKD severity, there is an inherent limitation of using a syndrome-based classification to discern differences in biochemistry parameters, and the limitation of using this diagnostic system in isolation needs to be recognized. On the other hand, we believe subtle changes in QoL may not be appreciated by measuring GFR in isolation, but the holistic and multi-system approach using TCM classification is better designed to detect changes in QoL parameters.

DKD is a multi-system disorder that causes not only higher mortality and morbidity but also significant impairment to the patient's QoL.[8,9] However, we found that categorizing patients into different DKD groups based on the CKD classification (i.e., using the GFR) managed to detect a statistically significant between-group difference in QoL in the physical function domain, but not the other domains.[8] Several reasons may explain our observation. First, QoL in the physical function domain is more severely affected in individuals with DKD relative to the other domains (reference). Second, impairment in QoL may not be detected until renal function becomes severely affected.[8] For example, impairment in QoL scores in an earlier study, measured using the same instrument as ours, only occurred when GFR was less than 45 ml/min/m^2.[9] Hence, the smaller number of patients with advanced CKD in our study may have limited the ability to detect impaired QoL scores in other domains. Interestingly, when subjects were categorized into different groups of DKD severity based TCM syndrome classification, between-group differences in QoL were detected in all eight QoL domains.

To the best of our knowledge, this is the first study to demonstrate the ability of TCM syndrome classification in detecting impaired QoL among patients with DKD. The ability to detect impaired QoL is essential in patients with DKD because poor QoL scores are

independent predictors of hospitalization and mortality.[21,22] Importantly, by detecting impaired QoL in patients with DKD early, healthcare providers have the opportunity to identify patients who require adjunctive treatment such as renal rehabilitation exercise programmes[23] or psychosocial support.[24] Our study also highlights the strengths and limitations of categorizing DKD severity using the CKD and TCM syndrome classification and the importance of integrating both systems to manage DKD effectively. Several studies highlighted this concept by demonstrating improvements in GFR and urine protein excretion in patients receiving both TCM herbal and Western medicine.[6,17,25] Most recently, a Taiwanese study also found that patients receiving both TCM and Western medicine treatment had the lowest risk of developing ESRD and mortality.[26]

Our study has several limitations. We planned this study with the exploratory intention to examine the ability of TCM syndrome classification to detect impairments in GFR and QoL. Hence, our study is not optimized to compare the performance of one classification system to another quantitatively. Suitably designed future studies are required to clarify this uncertainty. Further, future studies should also recruit adequate subjects in each ethnic group to examine the influence of ethnicity in TCM syndrome classification of DKD. In addition, we only recruited patients with stable DKD and the ability of TCM syndrome to diagnose more severe or alarming features of DKD need to be further examined. We did not use urine protein excretion to determine DKD severity. However, proteinuria or albuminuria is absent in many patients with DKD.[27,28] Our study was cross-sectional in design, and prospective studies are required to evaluate the ability of TCM syndrome classification in predicting DKD progression. We also utilised a generalised health questionnaire, and specific CKD questionnaire may be better in capturing all dimensions of QoL for DKD patients.

We conclude that TCM syndrome classification of DKD is capable of detecting differences in GFR and impairment in QoL across all domains in patients with DKD.

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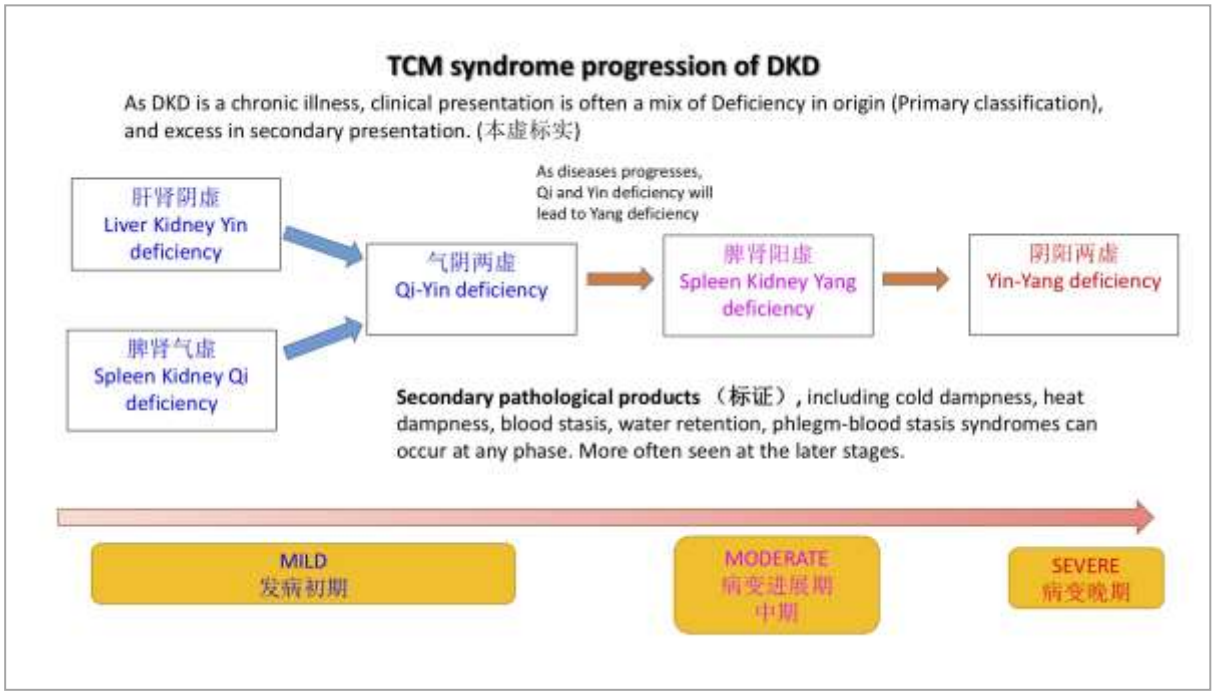


Figure 1 Categorization of diabetic kidney disease into stages of severity according to TCM syndrome classification

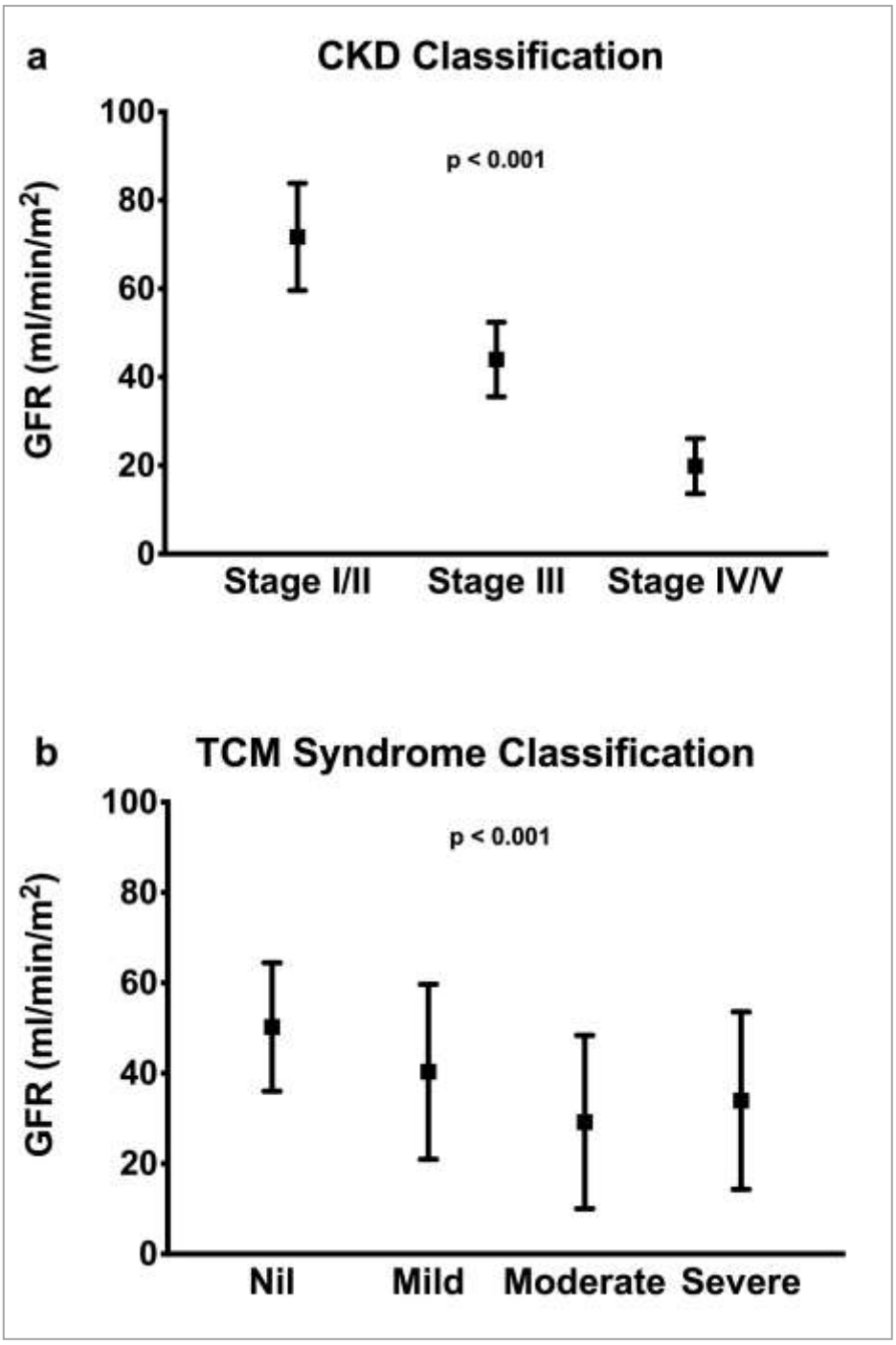


Figure 2 Glomerular filtration rates of subjects with diabetic kidney disease according to (a) CKD and (b) TCM syndrome classification
GFR = glomerular filtration rate. Between group differences was tested using ANOVA and a $p < 0.05$ considered as statistically significance

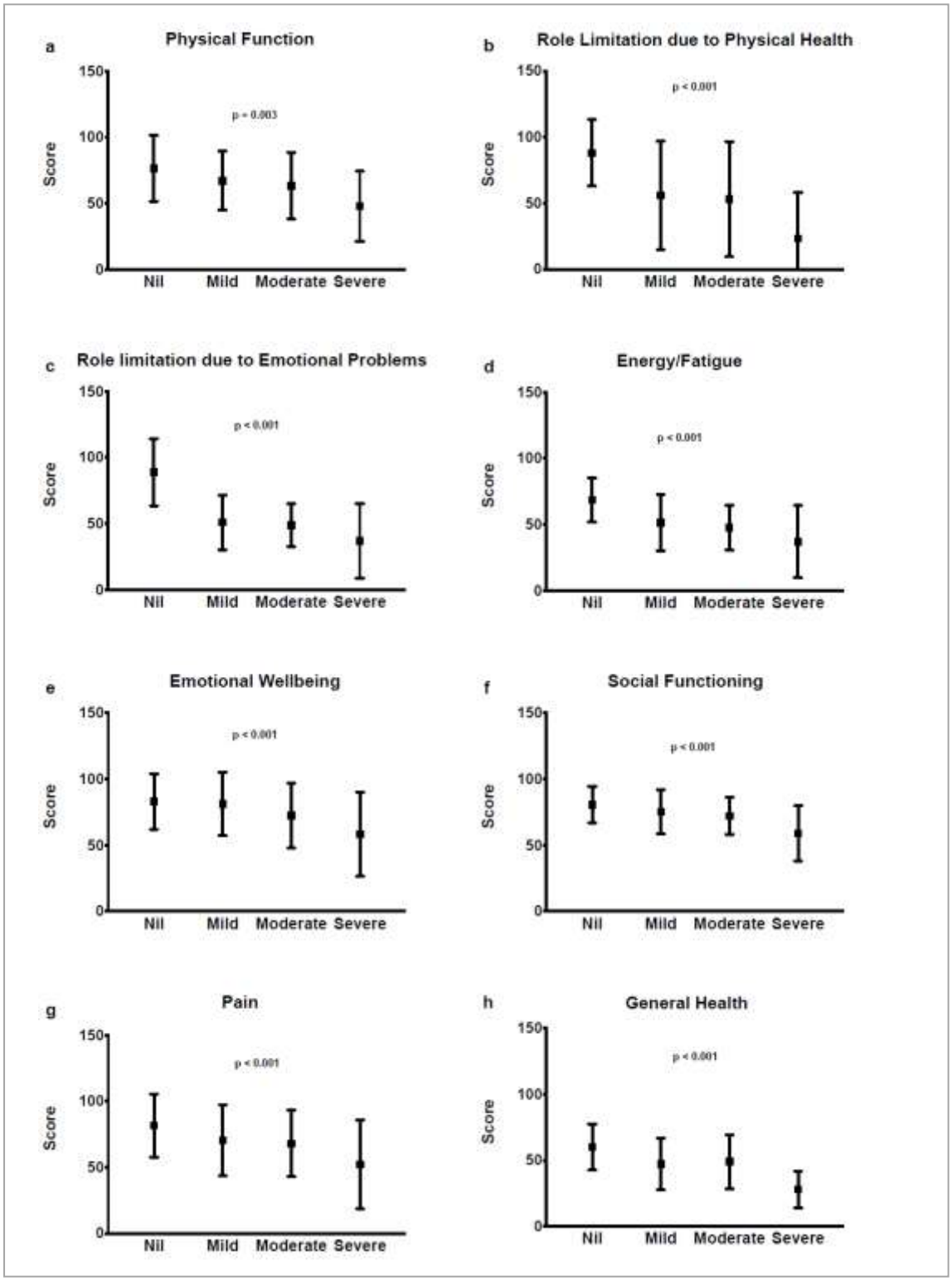


Figure 3 Quality of Life Scores of subjects with diabetic kidney disease according to TCM syndrome classification

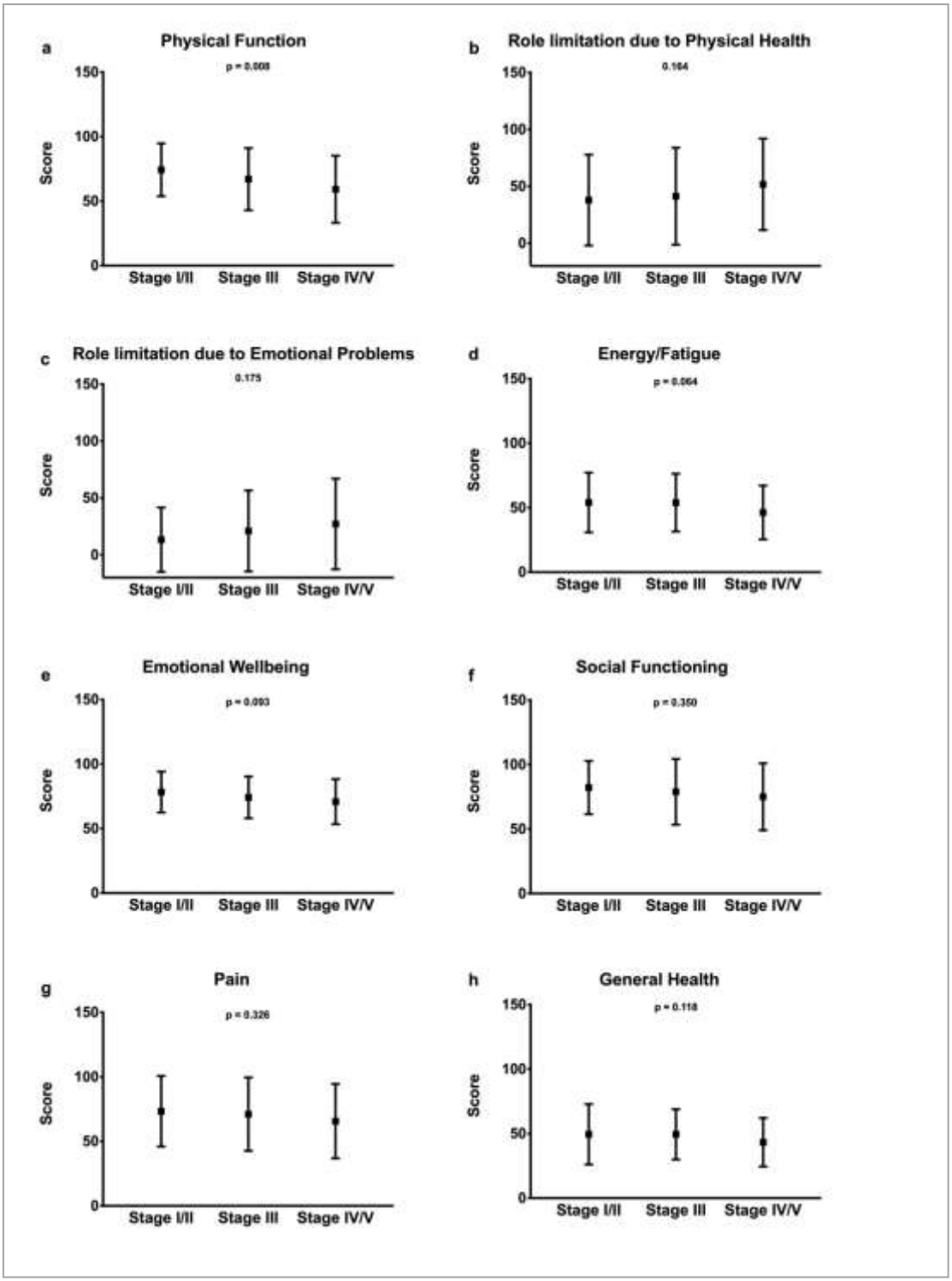
Quality of Life (QoL) were measured using the RAND-36 survey instrument and scores calculated for eight areas: (a) physical functioning, (b) role limitations due to physical health, (c) role limitations due to personal or emotional problems, (d) energy/fatigue, (e) emotional well-being, (f) social functioning, (g) pain and (h) general health. Between group differences was tested using ANOVA and a $p < 0.05$ considered as statistically significance.

APPENDIX

Supplementary Table 1 Baseline Characteristics of Subjects with Diabetic Kidney Disease

Characteristics	n = 200
Age* (years)	64 ± 8
Male (%)	61
Ethnicity (%)	
Chinese	76.0
Malay	12.0
Indians	10.5
Others	1.5
Duration of Diabetes* (years)	16.2 ± 8.3
Weight* (kg)	75.4 ± 14.6
Body mass index* (mg/kg^2)	28.4 ± 4.8
Systolic BP* (mmHg)	139 ± 23
Diastolic BP* (mmHg)	70 ± 10
HbA1C* (%)	8.3 ± 1.8
Lipid lowering medications (%)	92
Hypertension (%)	92
Blood pressure medications (%)	99
ACEi/ARB (%)	89.5
Others (%)	9.5
CKD Classification (%)	
Stage I/II	17.5
Stage III	46.0
Stage IV/V	36.5
TCM Syndrome Classification	(n=180)
Nil	13.9
Mild	62.8
Moderate	13.9
Severe	9.4

*Data presented as mean ± standard deviation. ACEi = angiotension-converting enzyme inhibitors, ARB = aldosterone receptor blockers, CKD = chronic kidney disease, TCM = Traditional Chinese Medicine



Supplementary Figure S1 Quality of Life Scores of subjects with diabetic kidney disease according to CKD Stages

Quality of Life (QoL) were measured using the RAND-36 survey instrument and scores calculated for eight areas: (a) physical functioning, (b) role limitations due to physical health, (c) role limitations due to personal or emotional problems, (d) energy/fatigue, (e) emotional well-being, (f) social functioning, (g) pain and (h) general health. Between group differences was tested using ANOVA and a $p < 0.05$ considered as statistically significance.