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Association between liver stiffness measurement by transient elastography and chronic kidney disease

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Abstract

Transient elastography or elastometry (TE) is widely used for clinically cirrhosis and liver steatosis examination. Liver fibrosis and fatty liver had been known to share some co-morbidities that may result in chronic impairment in renal function. We conducted a study to analyze the association between scores of 2 TE parameters, liver stiffness measurement (LSM) and controlled attenuation parameter (CAP), with chronic kidney disease among health checkup population.

This was a retrospective, cross-sectional study. Our study explored the data of the health checkup population between January 2009 and the end of June 2018 in a regional hospital. All patients were aged more than 18 year-old. Data from a total of 1940 persons were examined in the present study. The estimated glomerular filtration rate (eGFR) was calculated by the modification of diet in renal disease (MDRD-simplify-GFR) equation. Chronic kidney disease (CKD) was defined as eGFR < 60 mL/min/1.73 m^2.

The median of CAP and LSM score was 242, 265.5, and 4.3, 4.95 in non-CKD (eGFR > 60) and CKD (eGFR < 60) group, respectively. In stepwise regression model, we adjust for LSM, CAP, inflammatory markers, serum biochemistry markers of liver function, and metabolic risks factors. The *P* value of LSM score, ALT, AST, respectively is .005, $<.001$, and $<.001$ in this model.

The LSM score is an independent factor that could be used to predict renal function impairment according to its correlation with eGFR. This result can further infer that hepatic fibrosis may be a risk factor for CKD.

Abbreviations: γ-GT = gamma-glutamyl transpeptidase, ALK-P = alkaline phosphatase, BUN = blood urine nitrogen, CAP = controlled attenuation parameter, CKD = chronic kidney disease, DM = diabetes mellitus, eGFR = estimated glomerular filtration rate, FBS or glucose AC = fasting blood sugar, FPG = fasting plasma glucose, GOT = serum glutamic-oxaloacetic transaminase, HbA1C = hemoglobin A1c, HDL = high-density lipoprotein cholesterol, LSM = liver stiffness measurement, MDRD = modification of diet in renal disease, NAFLD = non-alcoholic fatty liver disease, TE = transient elastography or elastometry, TG = triglyceride, TMUH = Taipei Medical University Hospital, UA = uric acid.

Keywords: chronic kidney disease, Fibroscan, liver fibrosis, liver stiffness measurement, transient elastography

1. Introduction

Chronic kidney disease (CKD) has a high prevalence globally. The worldwide mean prevalence of 5 CKD stages is 13.4% and stages 3 to 5 is 10.6%.[1] In addition, Taiwan has the highest incidence and prevalence rates of end-stage renal disease globally.[2] Previous studies have reported that old age,[3–6] male sex,[5,7] diabetes mellitus (DM), hypertension, metabolic syndromes (MetS),[8] and advance liver fibrosis[9] are key risk factors for CKD.

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CSY and STW contributed equally to this work.

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There are numerous different methods and formula for estimating the glomerular filtration rate (eGFR) for the screening and staging of CKD. Most of the examination procedures require the collection of blood samples through phlebotomy, which is an invasive procedure. The liver stiffness measurement (LSM) by Fibroscan has been used extensively for the detection of liver fibrosis; however, so far, it has not been employed in the screening of CKD.

Recently, numerous studies have linked liver stiffness to CKD. CKD evaluated by the MDRD-6 estimated glomerular filtration rate equation was present in 46.0% of adult liver cirrhosis patients.[10] A review article illustrated mechanisms of kidney dysfunction in the cirrhotic patient. Such as nonalcoholic steatohepatitis (NASH), viral hepatitis, cardiovascular disease, and corticosteroid deficiency in cirrhotic patients can lead to both chronic and acute kidney damage.[11] In addition, a study using machine learning technologies, noted that LSM score, gamma-glutamyl transpeptidase (γGT), and GPT are the significant variables playing principal roles in CKD.[12] The value of the liver TE controlled attenuation parameter is also revealed the feasibility of predicting possible CKD-related diseases.[13]

We hypothesize that the prevalence of CKD among patients with cirrhosis has increased due to the increasing prevalence of CKD-associated comorbidities, such as diabetes, hypertension, and nonalcoholic fatty liver disease. CKD in cirrhosis can be structural CKD due to kidney injury or functional CKD secondary to circulatory and neurohormonal imbalances.[14]

However, the association between liver fibrosis level and CKD had not yet been well established. As known, cirrhotic patients frequently have comorbidities such as diabetes that may result in chronic impairment in renal function. Dexin Wang et al had reported that the incidence of impaired renal function has increased significantly with the deterioration of liver function in patients with cirrhosis.[15] Thus, we hypothesize that liver stiffness may be an independent factor that could be used to predict CKD.

TE, also called Fibroscan, was developed originally to assess the level of liver fibrosis based on a LSM score.[16–18] The underlying principle is the emission of low-frequency low-magnitude vibrations using probes, which deform the liver slightly and generate shear waves. Subsequently, sensors detect the conduction velocity under the skin, and tissue elasticity is calculated using a formula. In 2013, CAP was marketed as a novel measurement tool and for the quantification of liver steatosis.[19–22] Its theoretical basis is the intensity decay formula. The advantage of CAP is that it can measure and calculate the values of 2 indicators simultaneously and separately over the same scanning area compared with LSM.[19,22] The 2 parameters have been used extensively in clinical settings for the examination of liver fibrosis and steatosis in recent years. Because of its noninvasive attribute, individuals are more likely to be willing to undergo examinations.[23] For medical personnel, Fibroscan is convenient and facilitates the rapid acquisition of results. Fibroscan is also associated with a high reproducibility of its automatically quantitative assessment outputs across different operators.[24–26] In addition, 2 parameters, namely LSM and CAP, exhibit high sensitivity and specificity for liver fibrosis and hepatic steatosis, respectively.[27,28] Moreover, novel machine learning applications also reveal that LSM and CAP are potential factors to evaluate metabolic syndrome.[13,14,29] Therefore, the 2 parameters are appropriate screening tools for the determination of patient liver conditions in clinical contexts.

The aim of our study was to analyze the association between the values of 2 TE parameters (LSM, CAP), and CKD in health management settings.

2. Methods

2.1. Study design

This was a retrospective, cross-sectional study. This study explored the health checkup data of the participants who underwent a self-paid health examination between January 2009 and the end of June 2018 in Taipei Medical University Hospital (TMUH) Health Management Center (HMC). TMUH is a private teaching hospital which owned 800-bed in Taiwan. HMC of the TMUH receives 50 to 60 visits each day.

2.2. Sample size

Data from a total of 1940 persons, including 1874 non-CKD participants and 66 CKD participants, met the inclusion criteria and were examined in the present study.

2.3. Participant

To be included in the analysis, the participants' age must be above 18-year-old and have undergone a self-paid health examination comprising of an abdominal TE inspection by using Fibroscan 502 Touch (Echosense, Paris, France) and blood test for calculating eGFR. The excluding criteria is that the subject who lack of any data of variables including height, weight, waist circumference, eGFR, triglyceride, LDL-cholesterol, HDL-cholesterol, and fasting blood sugar (FBS or glucose AC) or did not undergo abdominal TE examination.

All of these participants' electronic medical records were reviewed and the data collection was administered by Chan YJ and Yu CS. During the research period, the code is used to replace the identification of the subject and the subject's privacy will not be leaked.

2.4. Issue of interest (exposure)

This study is aimed to compare the value of TE LSM and CAP between CKD (eGFR < 60) group and non-CKD (eGFR > 60) group and establish regression model for predicting CKD.

2.5. Comparison

TE LSM and CAP score in non-CKD (eGFR > 60) group.

2.6. Ethics and endpoint

The present study was conducted in line with the ethical standards of the Helsinki Declaration, and all data were from studies approved by the Institutional Review Board of Taipei Medical University Hospital (TMUH; TMU-JIRB approval number: N201903080). The Institutional Review Board has granted a waiver of informed consent due to the retrospective nature of this study.

2.7. Statistical analysis

Con nonparametric distributions are expressed as the median with interquartile range. Continuous variables were evaluated

Table 1

Demographic characteristics (non-CKD vs CKD).

Characteristic	Non-CKD (eGFR≥60)(N = 1874)[a]	CKD (eGFR < 60)(N = 66)[a]	*P* value (2-tail)
Age	44[36,51]	58.5[52,68.3]	<.001[†]
Male (total: 904)	864 (95.6%)	40 (4.4%)	.02[*]
Female (total:1036)	1010 (97.5%)	26 (2.5%)	
BMI	23.5[21.3,26]	25.2[23.1,27.7]	<.001[†]
WC	81[74,88]	88[82.9,94.6]	<.001[†]
TG	90[64,134]	142[87,169]	.001[†]
Total cholesterol	188[165,211]	190.5[153.8,220]	.731[†]
LDL	122[102,145]	123.5[95.75,156.5]	.485[†]
HDL	53[44,65]	45[36,53.3]	<.001[†]
HbA1C	5.3[5.1,5.6]	5.7[5.4,6.2]	<.001[†]
FPG	91[86,96]	97[90,106]	.001[†]
ALT	19[13,28.75]	19[15,26]	.793[†]
AST	20[17,25]	22 [17,27.3]	.034[†]
HBsAg (+) (total:215)	206 (95.8%)	9 (4.2%)	.503
HBsAg (-) (total:1723)	1666 (96.7%)	57 (3.3%)	
γ-GT	17[12,27]	23.5[18,38]	<.001[†]
Total bilirubin	0.6[0.4,0.8]	0.5[0.4,0.7]	.046[†]
ALK-P	60[50,73]	73.5[55,87]	<.001[†]
Uric acid	5.3[4.4,6.5]	7[5.9,8.2]	<.001[†]
Albumin	4.6[4.4,4.8]	4.5[4.2,4.7]	.002[†]
BUN	12[10,15]	20[16.8,25.3]	<.001[†]
LSM score (kPa)	4.3[3.5,5.1]	4.95[4.1,6.6]	<.001[†]
CAP score (db/m)	242[210,282]	265.5[230,307]	.008[†]

[a] Values are number (%), or median (interquartile range).

[*] The nominal scale is expressed as a percentage, and the Chi-Squared test is used to analyze whether there are statistically significant differences between 2 CKD groups.

[†] The ratio scale is expressed as the median [IQR], and the Mann–Whitney *U* test was used to analyze whether there are statistically significant differences between 2 CKD groups.

γ-GT = gamma-glutamyltransferase, ALK-P = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, BUN = blood urea nitrogen, FPG = fasting plasma glucose, GFR = glomerular filtration rate, HDL = high-density lipoprotein, LDL = low-density lipoprotein, TG = triglyceride, WC = waist circumference.

using visual (skewness, kurtosis, and histogram) and analytical methods, including the Kolmogorov–Smirnov test, to determine whether they had normal distributions. Categorical variables are summarized as frequencies (percentages), and their associations were analyzed using the Chi-Squared test. Differences in continuous variables between non-CKD and CKD groups in Table 1 were compared using the Mann–Whitney *U* test, and a *P* value of <.05 was considered statistically significant.

Table 2

Stepwise regression model.

Variables[b]	Standard error	*t*	*P* value
BUN	.130	−13.564	<0.001[a]
Uric acid	.401	−8.783	<0.001[a]
SBP	.035	−4.227	<0.001[a]
WBC	.188	5.128	<0.001[a]
WC	.063	−5.165	<0.001[a]
hs-CRP	2.412	−3.651	<0.001[a]
Cholesterol	.015	−2.708	.007[a]
HBsAg	1.614	−2.741	.006[a]
ALT	.049	5.739	<0.001[a]
AST	.080	−5.387	<0.001[a]
LSM score	.222	2.807	.005[a]
Fasting glucose	.031	−2.155	.031[a]

[a] $P < .05$, statistically significant.

[b] Variables enter in model: SBP, DBP, BMI, waist circumference, BUN, CPK, LDH, hs-CRP, TG, cholesterol, HDL, LDL, fasting glucose, HbA1C, AST, ALT, r-GT, ALK-P, total bilirubin, direct bilirubin, uric acid, WBC, RBC, HBsAg, anti-HCV, LSM score, CAP score.

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BUN = blood urea nitrogen, CAP = controlled attenuation parameter, DBP = diastolic blood pressure, HBsAg = hepatitis B surface antigen, hs-CRP = high-sensitivity C-reactive protein, LSM = liver stiffness parameter, SBP = systolic blood pressure, WBC = white blood cell, WC = waist circumference.

In Table 2, stepwise regression was used to establish prediction models for the determination of variables that influence eGFR greatly and to calculate their beta coefficient. A *P* value less than .05 was statistically significant. All the statistical analyses were conducted using IBM SPSS Statistics 25 (IBM Corp., Armonk, NY). Appropriate sample size was determined by the regression model under the setting of type 1 error (alpha) = 0.05, power = 0.8.[30]

2.8. The validity and reliability of the outcome measures

These self-paid health check-up patients are relatively healthy. All the examination process met the standard operating procedures, such as fasting for 8 hours before blood test, investigation for past medical history. If the patient did not met the criterion mentioned above, the patient will be excluded from the trial. Subjects with abnormal data will also be noted in the test records, and the patient is asked to come back and recheck

Venous blood samples were collected in vacuum tubes through venipuncture in the morning after a 12-hour fast; samples were stored at 4°C in a refrigerator before analysis in the hospital laboratory department. All blood analyses were performed in the clinical laboratory department of the regional hospital. Laboratories are certified by the College of American Pathologists. Urine specimens were obtained in the morning and scheduled to avoid menstruation events. Biochemical parameters measured in the laboratory included fasting plasma glucose (FPG), hemoglobin A1c (HbA1C), total cholesterol, triglyceride (TG), creatinine, blood urine nitrogen (BUN), albumin, total bilirubin, uric acid (UA), alkaline phosphatase (ALK-P), γ-GT, serum glutamic-oxaloacetic transaminase (GOT), serum glutamic-pyruvic

transaminase (GPT), high-density lipoprotein cholesterol (HDL) levels, and low-density lipoprotein cholesterol (LDL). The HbA1C level was measured using Capillarys 3 TERA (Sebia, France). The FPG level was measured using the hexokinase method. Cholesterol and TG levels were measured using an enzymatic colorimetric test, whereas the HDL level was measured using a selective-inhibition method. The other biochemical parameters were analyzed using a Cobas c702 automatic biochemical analyzer (Roche, Japan). Serum creatinine was measured by IDMS-equivalent test.

2.9. Definition of measurement cutoffs and calculations

CKD is defined by the 2012 KDIGO guidelines as abnormalities of kidney structure or function, present for more than 3 months, which have implications for health.[31] The estimated GFR (eGFR) was calculated using the modification of diet in the renal disease formula (MDRD-simplify-GFR) with the leading coefficient of 186. Variables in the MDRD formula include creatinine, age, and sex. According to National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) guidelines, chronic kidney disease has been defined as GFR < 60 mL/min/1.73 m^2 for $\geq$ 3 months, with or without kidney damage. Therefore, we separate our study population to 2 groups (non-CKD group and CKD group) by the criteria: eGFR ≥ 60 mL/min/1.73 m^2 and eGFR < 60 mL/min/1.73 m^2.

The LSM score was selected as the parameter for quantifying liver fibrosis severity. In addition, the controlled CAP was used to detect and quantify liver steatosis severity with the assistance of FibroScan 502 Touch (Echosense, Paris, France). The examination was performed using an M probe or an XL probe. The examination area was the right lobe of the liver through intercostal spaces with patients in dorsal decubitus and the right arm in maximal abduction. The adoption of the M probe (3.5 MHz) or the XL probe (2.5 MHz) was based on the recommendation of the instrumental auto-detection function.

The cut-off values were defined respectively by following LSM score: $\geq$7 kPa for F2, $\geq$9.5 kPa for F3, and $\geq$12.5 kPa for F4.[32] Besides, the hepatic steatosis were defined respectively by following CAP cut-off values: $\geq$238 dB/m was classified as S1 (corresponding to 11%–32% liver fat), $\geq$259 dB/m for S2 (33%–65% liver fat), and $\geq$292 dB/m for S3 ($\geq$66% liver fat).

TE examinations with $<$10 valid measurements, a success rate $<$60% and/or a ratio of the interquartile range of liver stiffness to the median value (IQR/M) $>$30% have been classified as unreliable.

3. Results

3.1. Study population

Table 1 presents the demographic characteristics of 1940 patients. Compared with patients with eGFR$\geq$60, patients with eGFR < 60 were more likely to be old, were male, and had higher waist circumference, BMI, TG, fasting glucose, HbA1C, GOT, γ-GT, ALK-P, BUN, and uric acid levels, in addition to higher LSM and CAP scores. Between the 2 groups, individuals with eGFR < 60 had the lower HDL and albumin level. Our results are consistent with previous research findings. Excluding LSM and CAP scores, factors listed above have been reported to be CKD risk factors or had relation to CKD.[33–35]

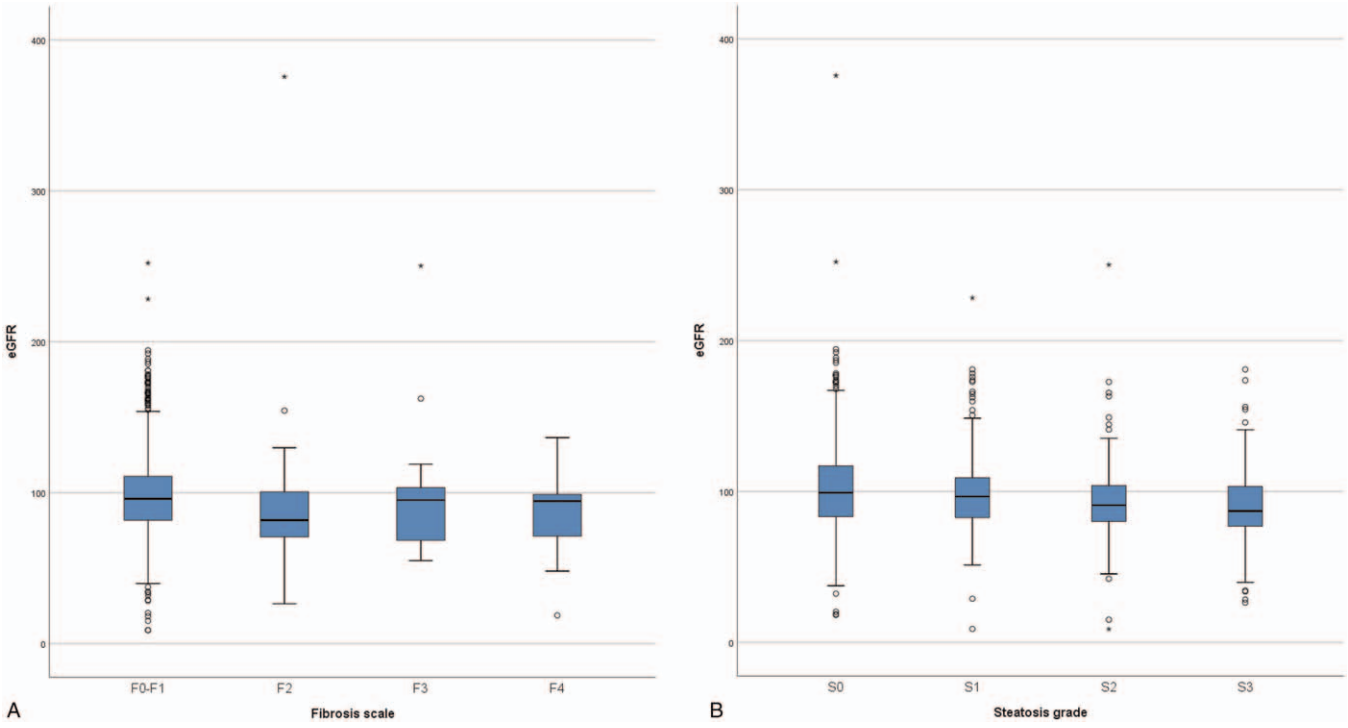

Figure 1. (A) Box plot: eGFR levels in 4 liver stiffness grades (F0-F1, F2, F3, F4)*. (B) Box plot: eGFR levels in four steatosis grades (S0, S1, S2, S3)**. In the box plots, the boundary of the box closest to zero indicates the 25th percentile, a black line within the box marks the median, and the boundary of the box farthest from zero indicates the 75th percentile. Points above and below the whiskers indicate outliers outside the 25th and 75th percentiles. *LSM cut-off values: $\geq$7 kPa for F2, $\geq$9.5 kPa for F3, and $\geq$12.5 kPa for F4. **CAP cut-off values: $\geq$238 dB/m was classified as S1, $\geq$259 dB/m for S2, and $\geq$292 dB/m for S3.

We examined the eGFR distributions of 4 fibrosis scale groups separately and presents in Figure 1A. Based on the graph and numerical measures, we can make the following comparison:

In F0-F1 group, half of the subjects eGFR is above 95.73. On the contrary, in F2, F3, and F4 groups, 75% of the subjects eGFR is below 101.7, 104.52, and 99.01. Besides, the mean, median, first quartile, and third quartile eGFR for F0-F1 group is higher than the other 3 groups. We therefore conclude that in general, the subjects in F0-F1 group have the highest eGFR than others.

Similarly, we can get some information according to Figure 1B. The median of eGFR decrease by the extent of liver stiffness stages. Besides, the mean, median, first quartile, and third quartile eGFR for S0 group is higher than the other 3 groups. We therefore conclude that in general, the subjects in S0 group have the highest eGFR than others.

3.2. Stepwise regression model for the prediction of eGFR

Table 2 displays the variables which can be predictive to eGFR. In the stepwise regression model, blood pressure, waist circumference, serum biomarker including BUN, uric acid, hsCRP, AST, ALT, HBsAg, cholesterol, fasting sugar, and Fibroscan LSM score are the best combination of variables to predict for eGFR. The *P* value of LSM score, ALT, AST respectively is .005, <.001, and <.001 in this model.

4. Discussion

Traditionally, CKD stages have been defined by only eGFR, an approach that is neither punctilious nor precise, because CKD is a progressive and complex disease. This is especially complicated in early stage CKD patients with a steep decline in their renal function. Therefore, it is challenging for clinicians to predict the progression of CKD and to identify early patient groups at risk of rapid deterioration within the same stage of CKD.

In a study conducted on patients with type 2 DM, liver fibrosis quantified using TE was not associated with an increased prevalence and severity of CKD.[36] Nevertheless, in a study examining an Asian NAFLD population, liver stiffness measured using TE was significantly higher in patients with CKD than in those without CKD. In addition, the area under the curve of liver stiffness was 0.694 (95% CI, 0.670–0.718), and a multivariable analysis of data identified 4 independent risk factors for CKD: age, diabetes mellitus, serum uric acid, and liver stiffness.[37] In our study, we provide another view. We found an increase in the LSM score implies a higher probability of a lower eGFR and we proposed a predictive model which include multiple risk factors. This can be useful to immediately evaluate cirrhotic patient whom may have high risk of CKD. The benefit of using LSM score to predict chronic kidney disease is that it does not need to follow the patient for 3 months.

Our stepwise regression model indicated that CAP scores is not the predictive variable to eGFR. However, based on Table 1, the CAP score medians were significantly different between 2 CKD groups. The reason could be due to our study population was relatively healthy, the prevalence of moderate to severe fatty liver is low. Besides, we also noticed other liver and biliary-related marker, such as AST ($P=.034$), γ-GT($P<.001$), total bilirubin ($P=.046$), ALK-P($P<.001$), albumin ($P=.002$) are statistically obvious related to CKD according to the Table 1.

A recent meta-analysis revealed that the sensitivity of LSM in detecting mild hepatic stiffness (F2) was 85% with a specificity of 79%, and the sensitivity of LSM in detecting moderate liver stiffness (F3) was 87% with a specificity of 84%. For severe liver stiffness (F4), the pooled sensitivity was 88% with a specificity of 91%.[27] In addition, LSM score and stiffness grades were highly positively correlated.[27] Therefore, based on the results of the present study, there is a correlation between the severity of hepatic stiffness and eGFR. And other studies also reveal that patients with severe liver diseases have abnormal creatinine and BUN outcomes.[38,39] However, there are some factors that would affect the evaluation performance for the liver stiffness by TE, such as the number of measurements, liver volumes, patient's conditions such as overweight or obesity or other complications as well as the fibrosis stage and experience of operators. Currently, it is generally agreed that 3 measurements are sufficient to obtain consistent results for assessing liver fibrosis.[26] Care should be exercised when applying the results in the condition noted above.

On the other hands, Tomasz et al noted the creatinine based estimates of GFR overestimate gold standard measured GFR (mGFR) in liver disease, and the degree of overestimation is highest at lower mGFR values and in more severe liver disease.[40]

4.1. The mechanism linking liver fibrosis and CKD

Advanced chronic liver disease is responsible for many physiological changes which affect the circulation and kidney perfusion. Severe liver fibrosis results in the accumulation of vasodilatory mediators, in particular nitric oxide, which specifically vasodilates the splanchnic circulation reducing the effective circulating blood volume and mean arterial pressure. Hypo-perfusion of the kidneys leads to a reduction in the sodium concentration of tubular fluid reaching the distal tubule stimulating the macular densa, to release renin, thus activating the renin-angiotensin-aldosterone (RAA) axis.[41] These factors may all have impact on the renal function.

4.2. Strength

A strength of our study is that the study population was relatively larger (N=1940) than the populations of previous studies.[11] In addition, the health-management database collected comprehensive information on all individuals whose data were extracted for the present study. In addition, we adjusted for multiple potential confounding factors, which have been demonstrated to be CKD risk factors using a regression model.

4.3. Limitations

The present study has some potential limitation. First, effect estimates in the model are based on retrospective cross-sectional studies. Therefore, the backgrounds of individuals could not be adjusted for adequately. Second, data were extracted from the database of a HMC. Most of the patients were relatively in healthy condition, and the CKD prevalence in our study group was lower than that in Taiwan. In addition, liver cirrhosis prevalence was low in the study population. Third, although 1940 participants were relatively adequate, data were limited to a single regional hospital. Therefore, data may be subject to

unknown degrees of bias. Therefore, more multi-center based studies are required to validate our findings.

5. Conclusion

According to the results of our study, the LSM score is an independent factor that could be used to predict eGFR. It means that Fibroscan hepatic LSM results can be used to not only evaluate liver stiffness but can also estimate the risk of chronic kidney disease. In addition, results suggest that liver stiffness may be a risk factor for CKD stage 3 to 5. Therefore, we suggest clinicians to instruct patients who have been diagnosed with early liver stiffness to improve their lifestyles, for example, engaging in adequate physical exercises and eating less greasy/starchy food, to prevent the development of advanced CKD. Future studies should focus on developing criteria for screening CKD; for instance, when the LSM score is above a certain cutoff, serum creatinine levels could be used to further screen CKD.

Author contributions

Conceptualization: Ya-Ju Chan, Shy-Shin Chang, Sen-Te Wang.
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Writing – original draft: Ya-Ju Chan.
Writing – review & editing: Ya-Ju Chan, Cheng-Sheng Yu.

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