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ORIGINAL RESEARCH

Associations Between Fatigue and Cardiovascular–Kidney–Metabolic Syndrome and the Mediating Role of Inflammation

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Purpose: Fatigue is common in many chronic diseases. The aim of this cross-sectional study was to investigate the association between fatigue and cardiovascular–kidney–metabolic syndrome (CKM) in Chinese asymptomatic individuals undergoing routine health screenings and to explore the mediating role of inflammation.

Patients and Methods: The data of 4349 individuals were included in this cross-sectional study. Fatigue was measured with the Fatigue Severity Scale (FSS). The association between fatigue and the severity of CKM syndrome was evaluated via logistic regression analysis. The mediating role of inflammation in fatigue and advanced CKM syndrome was explored using mediation analysis.

Results: A total of 4349 participants were included in this study, and 2120 (48.7%) experienced fatigue. Fatigue was associated with a greater risk of developing advanced CKM syndrome (OR 2.597, 95% CI 1.323–5.097, p <0.05). However, there was no significant correlation with the risk of developing early CKM syndrome. Further analyses stratified by age revealed that the association between fatigue and advanced CKM syndrome was more pronounced in those aged <60 years (OR 3.008, 95% CI 1.263–7.163, p <0.05). The white blood cell count and neutrophil count had a mediating effect in the association between fatigue and advanced CKM syndrome, with mediation rates of 7.2% and 6.3%, respectively.

Conclusion: Fatigue is significantly associated with the increased risk of advanced CKM syndrome, especially in young and middle-aged adults. The cause of this association may be that white blood cell count and neutrophil count play a partial role in this relationship.

Keywords: cardiovascular–kidney–metabolic syndrome, fatigue, inflammation, mediating effect

Introduction

Fatigue is a common chronic disease, manifesting itself as persistent fatigue and weakness accompanied by physical or mental impairment, and it can have a serious negative impact on patients' quality of life.[1,2] Approximately 45% of the United States population reports fatigue.[3] The prevalence of fatigue is 30% for men and 33.9% for women over 45 years of age in China.[4,5] Among perimenopausal and postmenopausal Chinese women, approximately 75.84% experienced fatigue.[6] Fatigue is likely to be overlooked by health care professionals during patient visits if there is a lack of targeted questioning.[7] Repeatedly ignoring fatigue tends to undermine the patient's medical experience and exacerbate misunderstandings about the patient by those around them, thus further contributing to social isolation and depressive symptoms.[2] Fatigue is associated with many diseases, including cancer, neurological disorders, psychiatric disorders, and metabolic disorders, and significantly increases the risk for developing negative health outcomes, but the mechanisms by which it occurs remain unclear.[8–11] Fatigue significantly increases the risk for developing negative health outcomes. A meta-

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analysis of clinical trials reported fatigue increased all-cause mortality in patients with chronic kidney disease (CKD).[12] A longitudinal study from Jerusalem residents reported that fatigue significantly increased the mortality among elderly people.[13] A study from Italy reported that fatigued men and women have an increased risk for disabilities.[14]

Obesity, diabetes, CKD and cardiovascular disease (CVD) continue to affect human health worldwide and are receiving increasing attention from researchers. The concept of cardiovascular–kidney–metabolic syndrome (CKM), proposed by the American Heart Association, is a systemic disease in which pathophysiological interactions between obesity, diabetes, chronic kidney disease, and cardiovascular disease lead to multiorgan dysfunction and adverse cardiovascular outcomes.[15] As CKM syndrome is a progressive disease, it gradually progresses from excess adipose tissue and dysfunction to a condition with multiple metabolic risk factors and promotes chronic kidney disease, which contributes to an increased risk of clinical cardiovascular disease, renal failure, disability and even death.[15] The CKM syndrome is classified into five stages: stage 0, no risk factors; stage 1, excess or dysfunctional adipose tissue; stage 2, metabolic risk factors and CKD; stage 3, subclinical CVD in CKM syndrome; stage 4, clinical CVD in CKM syndrome.[15] In the United States, nearly 90% of adults had CKM syndrome and 15% had advanced CKM syndrome.[16] Therefore, early detection and lifestyle intervention can help slow or even stop the progression of CKM.

Inflammation was considered as a potential factor in the development of fatigue.[17] A cohort study showed that inflammation may play a role in fatigue.[18] And it is a common view that inflammation plays a role in the progression of chronic diseases. The study on the syndrome of cardiometabolic disease reported that excess and dysfunctional adipose tissue exhibited inflammation, and increased the risk of CVD.[19] In addition, most previous research concentrated on a single disciplinary perspective and explored obesity, diabetes, CVD, and CKD separately. There has been insufficient co-operation between the different disciplines. And the links between the pathophysiological mechanisms of these diseases have been less well studied. Due to the lack of studies on pathophysiological mechanisms and the concept of CKM syndrome, the relationship between fatigue and CKM syndrome has not been adequately explored in prior studies. Therefore, on the basis of Chinese asymptomatic individuals undergoing routine health screenings at the Health Promotion Centre of Sir Run Run Shaw Hospital, this study assesses the correlation between fatigue and CKM syndrome and the potential mediating role of inflammatory markers between fatigue and advanced CKM syndrome, which may help promote early lifestyle management of CKM patients.

Materials and Methods

Study Population

All subjects in this cross-sectional study completed a systematic health check-up and standardized questionnaires. Data were collected between September 2024 and December 2024 at Sir Run Run Shaw Hospital, Zhejiang University School of Medicine. The inclusion criterion was being over 18 years of age (n=5001). The exclusion criteria were participants who lacked data on past history, smoking history, alcohol consumption, height, weight, waist circumference, and blood pressure (n=416) or those with missing blood metabolism indicators and questionnaire data (n=225). Participants who submitted multiple health questionnaires (n=11) were excluded. A final total of 4349 participants were included in the analysis. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Sir Run Run Shaw Hospital, affiliated with Medical College of Zhejiang University (No. 2025–1033).

Data Collection

During the health screening, participants' sex, age, history of previous illnesses and medications, smoking history, and alcohol consumption history were collected by trained general practitioners through face-to-face interviews. The participants completed an assessment of the Fatigue Severity Scale (FSS) via an online structured questionnaire. Nurses measured systolic blood pressure (SBP), and diastolic blood pressure (DBP), waist circumference (WC) from participants using calibrated standard instruments. Venous blood samples were taken in the morning after an overnight fast. Body mass index (BMI) was calculated by dividing body weight by the square of the elevation. The estimated glomerular filtration (eGFR) rate was calculated according to the race-free CKD-EPI 2021 creatinine formula.[20]

Definition of Fatigue

Fatigue was defined and assessed on the basis of the FSS score. The scale is validated in healthy individuals and patients with multiple medical conditions, including patients with multiple sclerosis, systemic lupus erythematosus, and chronic stroke.[21–24] The scale is a 9-item self-report scale to assess the severity of fatigue. Respondents are asked to consider the previous week and rate each statement on a Likert scale from 1 (strongly disagree) to 7 (strongly agree).[23] The FSS score was the total score divided by 9, where fatigue was defined as an FSS score ≥4.[25] On the basis of the quartiles of the FSS scores, the participants were divided into four groups: Q1 (1.0–3.0), Q2 (3.0–3.9), Q3 (3.9–4.6), and Q4 (4.6–7.0). Q1 was used as the reference group.

Definition of CKM Syndrome

CKM syndrome is divided into 5 stages on the basis of the recommendations of the President of the American Heart Association.[15] CKM Stage 0 is defined as the absence of excessive/dysfunctional obesity, metabolic risk factors and chronic kidney disease. CKM stage 1 is defined as overweight/obesity (BMI ≥24 kg/m^2), abdominal obesity (WC ≥80 cm for women and ≥90 cm for men) or prediabetes (defined as a glycosylated haemoglobin [$HbA1_C$] 5.7–6.4% or a fasting plasma glucose [FPG] between 5.6–6.9 mmol/L, without a self-reported diagnosis of diabetes). CKM stage 2 is defined as metabolic risk factors or intermediate to high risk of CKD (based on eGFR). Metabolic risk factors include hypertriglyceridaemia (triglyceride [TG] ≥1.53mmol/L), hypertension (SBP≥140mmHg or DBP≥90mmHg), type 2 diabetes mellitus (defined as HbA1C ≥6.5%, or FPG ≥7.0 mmol/L, or a past history of diabetes), or metabolic syndrome. CKM stage 3 is defined as combined subclinical cardiovascular disease on the basis of a predicted 10-year CVD risk of ≥20% in the AHA's Predicting Risk of CVD EVENTs (PREVENT) equation (https://professional.heart.org/en/guidelines-and-statements/prevent-calculator). CKM stage 4 is defined as a combination of clinical cardiovascular disease based on a previous history of cardiovascular disease.

Metabolic syndrome is defined by the presence of 3 or more of the following: WC ≥80 cm for women and ≥90 cm for men; High-density lipoprotein cholesterol (HDL-C) <1.04 mmol/L for men and <1.30 mmol/L for women; TG ≥1.70 mmol/L; SBP ≥130 mmHg or DBP ≥80 mmHg or use of antihypertensive medications; FPG ≥5.6 mmol/L.[15]

In accordance with AHA recommendations, in this study, CKM stages 1 and 2 were combined as early CKM syndrome, and stages 3 or 4 were combined as advanced CKM syndrome.[16] Advanced CKM syndrome staging identifies people who have CVD or are at high risk of CVD.[16]

Definition of Inflammation

Fasting venous blood samples were selected to collect systemic immunoinflammatory index (SII), neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR). The SII is the platelet count multiplied by the neutrophil count divided by the lymphocyte count. All indicators of inflammation were converted to natural logarithmically transformed values.

Assessment of Variables

Categorical variables consisted of sex, smoking and alcohol consumption, previous history of diabetes, and previous history of hypertension. Age, BMI, WC, SBP, DBP, total cholesterol (TC), TG, FPG, HbA1c, blood urea nitrogen (BUN), creatinine (Cr), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), serum uric acid (SUA), and eGFR were analysed as continuous variables.

Statistical Analysis

Analyses were performed using SPSS version 25 software and R version 4.4.2. In this study, quantitative variables are expressed as the means±standard deviations or medians (interquartile ranges). Differences were assessed using an independent samples *t* test or Mann–Whitney *U*-test and ANOVA or K independent samples test. Qualitative variables were expressed as percentages and were assessed using the chi-square test. The normality test was assessed by Kolmogorov–Smirnov test. Correlation analysis between fatigue and CKM syndrome was assessed using logistic regression. Multicollinearity was assessed using the Pearson's correlation coefficient and the Variance Inflation Factor.

The model fit was assessed by the Hosmer–Lemeshow goodness-of-fit Chi-square test. And the result was presented as the odds ratio (OR) and the 95% confidence interval (CI). Model 1 was not adjusted. Model 2 was adjusted for age, sex, smoking status, drinking status, BMI, WC, SBP, and DBP. Further analyses were stratified by age. Excluding participants with cancer history, sensitivity analysis was conducted to test the robustness of the results. Mediation analysis was used by causal steps approach, to assess the impact of inflammatory markers on the development of advanced CKM syndrome in fatigued patients. The level of statistical significance was set at $p < 0.05$.

Results

The baseline characteristics of the included participants are summarized in Table 1. There were 4349 participants, including 2683 (61.7%) men and 1666 (38.3%) women. A total of 2120 (48.7%) patients had fatigue. There were no significant differences between the fatigued and nonfatigued populations in terms of BMI, WC, smoking status, or TC, TG, LDL-c, FPG, HbA1c, or SUA levels. The data indicate that those with fatigue had a lower average age, SBP, DBP,

Table 1 The Baseline Characteristics of Included Participants

Characteristics	ALL	Fatigue		*p* Value
	(N=4349)	NO (N=2229)	YES (N=2120)	
Demographic Characteristic				
Gender,N(%)				0.082
Males	2683(61.7)	1403(62.9)	1280(60.4)	
Females	1666(38.3)	826(37.1)	840(39.6)	
Age, year	37(31,45)	38(31,46)	36(30,43)	<0.001*
BMI,kg/m^2	24.06±3.60	24.01±3.46	24.11±3.75	0.363
WC,cm	81.86±10.90	81.75±10.62	81.97±11.18	0.514
SBP,mmHg	120.97±15.74	121.55±16.04	120.35±15.40	0.011*
DBP,mmHg	73.31±10.94	73.66±10.96	72.93±10.91	0.028*
Smoking,N(%)	779(17.9)	397(17.8)	382(18.0)	0.858
Drinking,N(%)	1573(36.2)	854(38.3)	719(33.9)	0.003*
Inflammation				
White blood cell count	1.75±0.24	1.73±0.24	1.77±0.24	<0.001*
Neutrophil count	1.18±0.31	1.16±0.31	1.21±0.31	<0.001*
Lymphocyte count	0.63±0.27	0.63±0.27	0.64±0.27	0.036*
Platelet count	5.47±0.22	5.46±0.21	5.48±0.23	0.003*
SII	6.02±0.42	6.00±0.41	6.05±0.43	<0.001*
NLR	0.55±0.36	0.53±0.35	0.56±0.36	0.014*
PLR	4.84±0.30	4.84±0.30	4.84±0.31	0.824
TC, mmol/L	5.06±1.01	5.08±0.96	5.04±1.05	0.151
TG, mmol/L	1.18(0.83,1.78)	1.17(0.83,1.77)	1.19(0.84,1.80)	0.323
LDL-c, mmol/L	3.19±0.70	3.20±0.70	3.18±0.71	0.252
HDL-c, mmol/L	1.30±0.31	1.31±0.31	1.29±0.30	0.014*
FPG,mmol/L	5.00±0.81	4.98±0.76	5.01±0.86	0.182
HbA1c,%	5.38±0.61	5.36±0.57	5.40±0.66	0.144
Cr, umol/L	73.64±14.70	74.29±14.65	72.96±14.72	0.003*
BUN,mmol/L	5.05±1.17	5.10±1.17	4.99±1.16	0.003*
SUA,umol/L	365.47±93.05	366.20±91.18	364.69±94.99	0.592
eGFR, mL/min/1.73m^2	104.63±13.49	103.58±13.75	105.73±13.13	<0.001*
Diabetes,N(%)	183(4.2)	89(4.0)	94(4.4)	0.469
Hypertension,N(%)	745(17.1)	401(18.0)	344(16.2)	0.123
MetS,N(%)	840(19.3)	417(18.7)	423(20.0)	0.299
Cancer,N(%)	116(2.7)	59(2.6)	57(2.7)	0.932

(*Continued*)

Table 1 (Continued).

Characteristics	ALL	Fatigue		*p* Value
	(N=4349)	NO (N=2229)	YES (N=2120)	
CKM syndrome stage,N(%)				
Stage 0	1544(35.5)	792(35.5)	752(35.5)	0.967
Stage 1	907(20.9)	458(20.5)	449(21.2)	0.608
Stage 2	1848(42.5)	959(43.0)	889(41.9)	0.467
Stage 3	27(0.6)	16(0.7)	11(0.5)	0.404
Stage 4	23(0.5)	4(0.2)	19(0.9)	0.001*

Note: *$p<0.05$.

Abbreviations: BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; SII, Neutrophil count × platelet count / lymphocyte count; NLR, neutrophil-lymphocyte ratio; PLR, platelet–lymphocyte ratio; TC, total cholesterol; TG, triglyceride; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; FPG, fasting plasma glucose; $HbA1_C$, glycosylated haemoglobin; Cr, creatinine; BUN, blood urea nitrogen; SUA, serum uric acid; MetS, Metabolic syndrome; CKM, cardiovascular–kidney–metabolic syndrome.

HDL-c, Cr, and BUN and had a higher eGFR (*p* values less than 0.05). The prevalence of CKM syndrome with respect to fatigue status across different age groups is shown in Table 2. We found a greater prevalence of advanced CKM syndrome among fatigued patients aged <60 years.

The associations between fatigue and CKM syndrome stages are displayed in Table 3. After adjustment for confounders in Model 2, fatigued patients had an increased risk of advanced CKM syndrome compared with patients without fatigue (OR 2.597, 95% CI 1.323–5.097, p=0.006), while there was no significant correlation with the risk of developing early CKM syndrome (OR 0.994, 95% CI 0.831–1.190, p=0.952). The FSS score was positively correlated with the risk of advanced stages (OR 1.405, 95% CI 1.081–1.827, p=0.011), but not with the risk of early CKM syndrome (OR 1.033, 95% CI 0.959–1.112, p=0.390). Compared with patients with FSS scores ≤3.0, patients with FSS scores of 3.9–4.6 had an increased risk of advanced stages (OR 3.328, 95% CI 1.407–7.870, p=0.006). Further analysis stratified by age revealed that the association between fatigue and advanced stages was more significant in those aged <60 years (OR 3.008, 95% CI 1.263–7.163, p=0.013), although the results of the interaction test were not distinct (p for interaction>0.05), as shown in Figures 1 and 2. Sensitivity analyses are displayed in Table 4. After excluding participants with cancer history, the relationship between fatigue and CKM syndrome stages showed similar results.

The mediating effects of inflammatory indicators in fatigue and advanced CKM syndrome is shown in Figure 3. After adjusting for Model 2, white blood cell count and neutrophil count had a mediating effect on the association between fatigue and advanced stages, with mediating proportions of 7.2% and 6.3%, respectively.

Table 2 The Prevalence of CKM Syndrome in Fatigue Statues in Different Age Levels

	CKM Syndrome Stage			
	Stage 0	Stage 1–2	Stage 3–4	*p*
Fatigue				
All	752(48.7%)	1338(48.6%)	30(60.0%)	0.276
Age<60	743(48.7%)	1297(49.0%)	20(74.1%)	0.032*
Age≥60	9(52.9%)	41(37.3%)	10(43.5%)	0.440

Note: *$p<0.05$.

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Table 3 The Association Between Fatigue and CKM Syndrome Stages

	Model 1		Model 2	
	OR (95% CI)	***p***	**OR (95% CI)**	***p***
CKM syndrome Stage 1–2				
Fatigue				
No	Reference		Reference	
Yes	0.980(0.867,1.109)	0.754	0.994(0.831,1.190)	0.952
Continuous FSS scores	0.981(0.933,1.032)	0.461	1.033(0.959,1.112)	0.390
FSS-Q1	Reference		Reference	
FSS-Q2	1.050(0.883,1.248)	0.583	1.118(0.871,1.436)	0.381
FSS-Q3	1.009(0.849,1.199)	0.918	0.927(0.721,1.192)	0.556
FSS-Q4	0.997(0.840,1.184)	0.975	1.185(0.921,1.524)	0.186
CKM syndrome Stage 3-4				
Fatigue				
No	Reference		Reference	
Yes	1.585(0.898,2.800)	0.112	2.597(1.323,5.097)	0.006*
Continuous FSS scores	1.080(0.860,1.355)	0.507	1.405(1.081,1.827)	0.011*
FSS-Q1	Reference		Reference	
FSS-Q2	0.744(0.303,1.827)	0.519	1.219(0.440,3.381)	0.703
FSS-Q3	1.894(0.922,3.894)	0.082	3.328(1.407,7.870)	0.006*
FSS-Q4	0.912(0.392,2.119)	0.830	2.151(0.799,5.791)	0.130

Notes: *p<0.05. The quartiles of FSS scores were calculated respectively (FSS-Q1 1.0–3.0, FSS-Q2 3.0–3.9, FSS-Q3 3.9–4.6, and FSS-Q4 4.6–7.0). Model 1 was not adjusted. Model 2 was adjusted for age, sex, smoking status, drinking status, BMI, WC, SBP, and DBP.

Discussion

This study investigated the correlation between fatigue and CKM syndrome in Chinese asymptomatic individuals undergoing routine health screenings. Fatigue was found to be positively correlated with advanced CKM syndrome but not with early CKM syndrome. FSS scores were positively correlated with advanced stages but not with early CKM syndrome. This correlation was significant in the young and middle-aged populations. In addition, mediation effect analysis further demonstrated that blood cell count and neutrophil count mediated the association between fatigue and advanced stages (7.2% and 6.3%, respectively).

Few previous studies have focused on the correlation between fatigue and CKM syndrome. Keyu Bian et al reported that fatigue was associated with an increased risk of stroke, coronary artery disease, type 2 diabetes and heart failure.[9] Yasuyuki Honda et al reported that fatigue was associated with an increased risk of peripheral arterial disease.[26] Studies by Charlotte Winwards et al, Peter Appelros, Eva-Lotta Glader and others revealed a significant positive correlation between fatigue and stroke.[27–29] Amber J. Guest et al reported that fatigue is negatively correlated with systolic and diastolic blood pressure.[30] L. Parker Gregg et al reported that fatigue in dialysis-dependent kidney disease patients was independently associated with the progression of end-stage renal disease.[31] However, there are still no uniform conclusions in studies on the correlation between fatigue and diabetes. Some studies have shown increased levels of fatigue in

Subgroup	Fatigue	OR(95% CI)	p	p for interaction
Age<60	Fatigue			
	no	Reference		
	yes	1.001(0.831,1.206)	0.988	
Age≥60	Fatigue			
	no	Reference		
	yes	0.581(0.254,1.330)	0.199	0.297
Age<60	Continuous FSS scores	1.030(0.953,1.112)	0.457	
	FSS-Q1	Reference		
	FSS-Q2	1.066(0.823,1.381)	0.627	
	FSS-Q3	0.911(0.701,1.182)	0.482	
	FSS-Q4	1.169(0.900,1.516)	0.241	
Age≥60	Continuous FSS scores	0.971(0.718,1.313)	0.850	
	FSS-Q1	Reference		
	FSS-Q2	1.781(0.525,6.039)	0.354	
	FSS-Q3	0.685(0.234,2.008)	0.491	
	FSS-Q4	0.728(0.239,2.222)	0.577	0.572

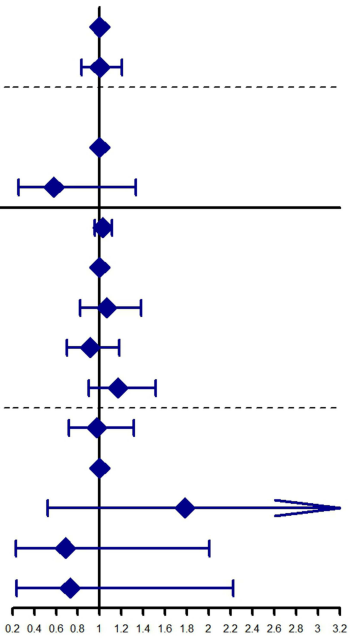

Figure 1 Adjusted odd ratios for CKM syndrome Stage 1–2 with fatigue by using model 2. The quartiles of FSS scores were calculated respectively (FSS-Q1 1.0–3.0, FSS-Q2 3.0–3.9, FSS-Q3 3.9–4.6, and FSS-Q4 4.6–7.0). Model 2 was adjusted for age, sex, smoking status, drinking status, BMI, WC, SBP, and DBP.

Subgroup	Fatigue	OR(95% CI)	p	p for interaction
Age<60	Fatigue			
	no	Reference		
	yes	3.008(1.263,7.163)	0.013	
Age≥60	Fatigue			
	no	Reference		
	yes	1.037(0.333,3.231)	0.950	0.524
Age<60	Continuous FSS scores	1.377(1.009,1.880)	0.044	
	FSS-Q1	Reference		
	FSS-Q2	1.509(0.334,6.806)	0.593	
	FSS-Q3	5.494(1.576,19.149)	0.007	
	FSS-Q4	1.878(0.443,7.958)	0.392	
Age≥60	Continuous FSS scores	0.936(0.583,1.502)	0.785	
	FSS-Q1	Reference		
	FSS-Q2	0.298(0.054,1.627)	0.162	
	FSS-Q3	0.402(0.080,2.011)	0.267	
	FSS-Q4	1.101(0.226,5.351)	0.905	0.134

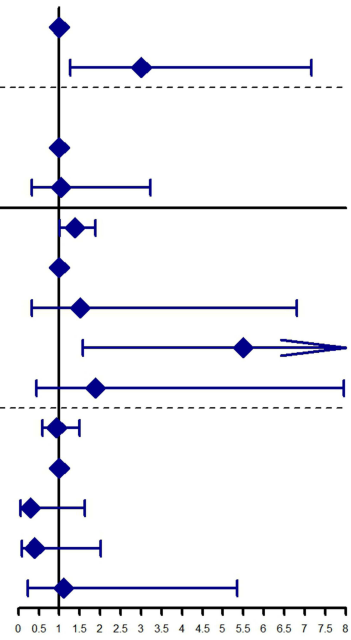

Figure 2 Adjusted odd ratios for CKM syndrome Stage 3–4 with fatigue by using model 2. The quartiles of FSS scores were calculated respectively (FSS-Q1 1.0–3.0, FSS-Q2 3.0–3.9, FSS-Q3 3.9–4.6, and FSS-Q4 4.6–7.0). Model 2 was adjusted for age, sex, smoking status, drinking status, BMI, WC, SBP, and DBP.

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Table 4 The Association Between Fatigue and CKM Syndrome Stages Excluding Patients with Cancer History

	Model 1		Model 2	
	OR (95% CI)	***p***	**OR (95% CI)**	***p***
CKM syndrome Stage 1–2				
Fatigue				
No	Reference		Reference	
Yes	0.970(0.856,1.099)	0.630	0.983(0.819,1.179)	0.853
Continuous FSS scores	0.976(0.927,1.027)	0.341	1.028(0.954,1.108)	0.468
FSS-Q1	Reference		Reference	
FSS-Q2	1.017(0.853,1.212)	0.853	1.103(0.855,1.422)	0.451
FSS-Q3	0.978(0.821,1.165)	0.803	0.897(0.695,1.158)	0.404
FSS-Q4	0.977(0.821,1.162)	0.791	1.180(0.914,1.523)	0.204
CKM syndrome Stage 3-4				
Fatigue				
No	Reference		Reference	
Yes	1.586(0.898,2.802)	0.112	2.627(1.338,5.161)	0.005*
Continuous FSS scores	1.080(0.860,1.356)	0.507	1.402(1.079,1.823)	0.011*
FSS-Q1	Reference		Reference	
FSS-Q2	0.745(0.304,1.831)	0.522	1.205(0.434,3.343)	0.720
FSS-Q3	1.897(0.923,3.901)	0.082	3.379(1.426,8.006)	0.006*
FSS-Q4	0.913(0.393,2.122)	0.832	2.147(0.797,5.783)	0.131

Notes: *$p<0.05$. The quartiles of FSS scores were calculated respectively (FSS-Q1 1.0–3.0, FSS-Q2 3.0–3.9, FSS-Q3 3.9–4.6, and FSS-Q4 4.6–7.0). Model 1 was not adjusted. Model 2 was adjusted for age, sex, smoking status, drinking status, BMI, WC, SBP, and DBP.

diabetic patients.[32,33] A review revealed that acute hypoglycaemia or chronic hyperglycaemia or fluctuations in blood glucose due to abnormal glucose metabolism in patients with diabetes may affect fatigue symptoms.[34] Julie Lasselin et al reported no correlation between fatigue and glycated haemoglobin in diabetic patients.[35]

We found that fatigue was positively correlated with advanced CKM syndrome but was not correlated with early CKM syndrome and that this correlation was significant in young and middle-aged individuals. The possible mechanism is the involvement of fatigue in the common pathophysiological effects of advanced stages. Fatigue production is associated with activated immunoinflammatory pathways, elevated levels of oxidative stress and mitochondrial dysfunction.[36–38] Fatigue may be involved in sympathetic overactivity, the renin–angiotensin–aldosterone system, and oxidative stress in CKM syndrome.[39] Early CKM syndrome is associated mainly with metabolic risk factors, including BMI, WC, fasting glucose, glycation, blood pressure, triglycerides and renal disease, and the probable reason for this result is that the present study population consisted mainly of young and middle-aged individuals. In addition, work and economic stress are more common in middle-aged individuals with chronic diseases, which may further contribute to the development of fatigue.[40] This prompts the early introduction of targeted lifestyle changes to improve symptoms of fatigue in young and middle-aged people.

Furthermore, we investigated the mediating role of white blood cell count and neutrophil count in the association of CKM syndrome and fatigue. Inflammation has been suggested as a possible mechanism influencing the development of

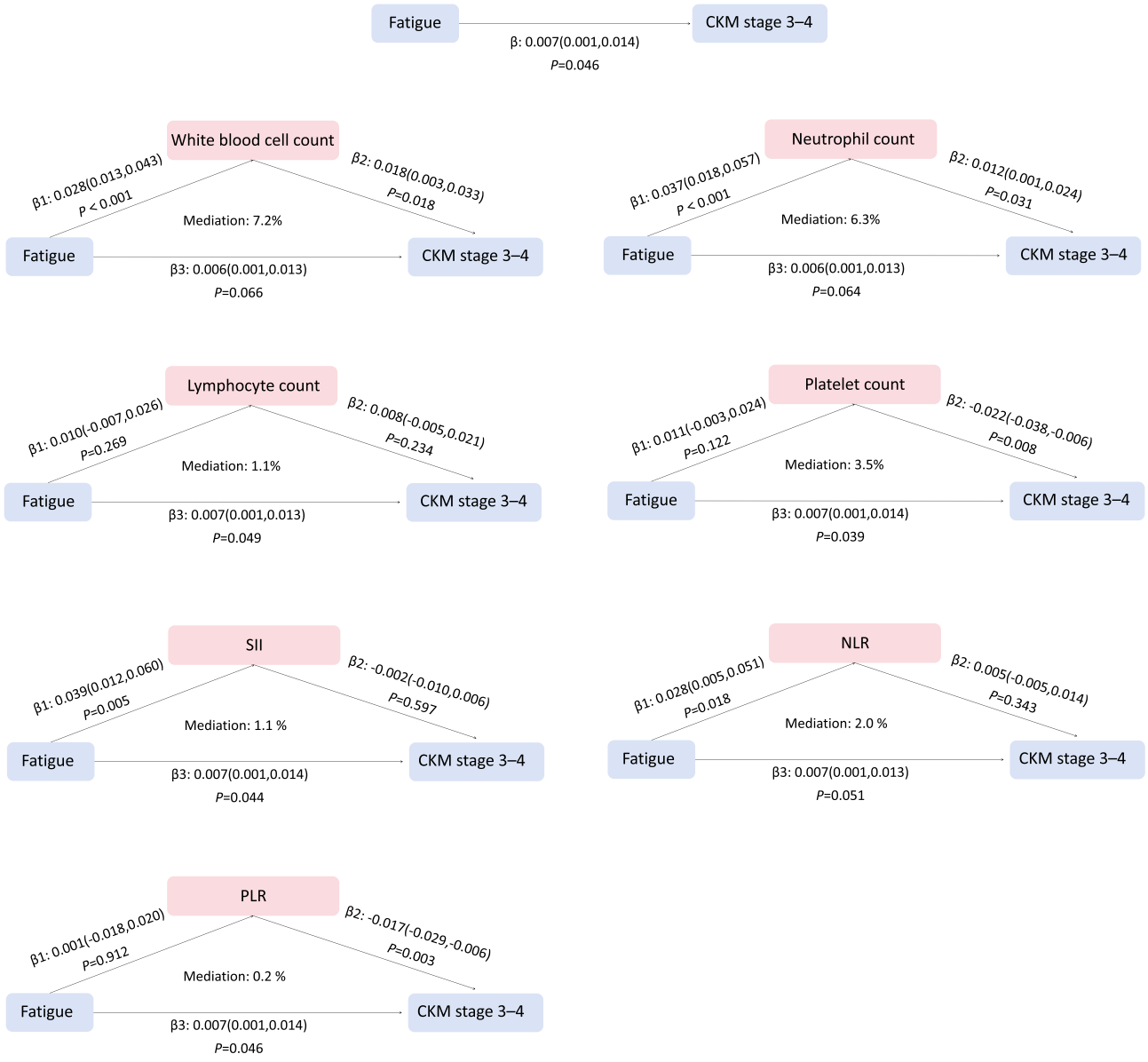

Figure 3 The mediating effects of inflammatory indicators in fatigue and advanced CKM syndrome with adjusting for Model 2.
Abbreviations: SII, systemic immunoinflammatory index; NLR, neutrophil/lymphocyte ratio; PLR; platelet/lymphocyte ratio.

fatigue, and studies have shown that fatigue is associated with chronic inflammation, which affects the peripheral and central nervous systems.[41] In advanced stages, endothelial dysfunction is further exacerbated by increased oxidative stress, increasing the risk of CVD.[39] In addition, dysfunction of the autonomic nervous system and dysregulation of the hypothalamic–pituitary–adrenal axis also increase the risk of CVD.[42] The role of inflammatory mediators is further supported by a study showing that an elevated systemic inflammatory response index was associated with an increased risk of cardiovascular disease mortality, which was evident in people under 60 years of age.[43]

As a cross-sectional study, the results of this study preclude causal inferences. We could not explore the causal relationship between fatigue and CKM syndrome. Second, our assessment of fatigue was based on the content of the questionnaire, which may be affected by self-report bias. Furthermore, as a single-dimensional scale, the FSS can not systematically evaluate different dimensions of fatigue, and it cannot capture multiple features of fatigue and its impact on function. Finally, the study population was mainly the health check-up population in Zhejiang Province, China, and may not reflect other populations. The Fatigue Severity Scale should be included in the early screening of CKM

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syndrome, which may contribute to identifying and mitigating the progression of the disease. In the future prospective cohort study, we can further study the role of inflammatory indicators such as C-reactive protein in fatigue and CKM syndrome in different CKM stages.

Conclusion

In the asymptomatic individuals undergoing routine health screenings, people with fatigue are correlated with a greater risk of developing advanced CKM syndrome, especially young and middle-aged people. It is clear that while inflammation appears to play a role, it only partially explains the observed association. In the early screening of CKM syndrome, the implementation of fatigue assessment should be emphasized. Individuals with fatigue should accept interdisciplinary care early and address adverse social determinants of health actively.

Data Sharing Statement

The datasets analysed during the current study are not publicly available because the data of this study was retrospective and informed consent could not be obtained, so the exemption of informed consent was applied. In order to respect the study subjects, this research data cannot be shared with others.

Ethics Approval and Consent to Participate

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Sir Run Run Shaw Hospital, affiliated with Medical College of Zhejiang University (No. 2025-1033). Patient consent was waived due to the research using the data obtained in the previous clinical diagnosis and treatment, without using the medical records that the patient has clearly refused to use. The study will not adversely affect the rights and health of the subjects, and the privacy and personal identity of the subjects will be protected.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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