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Original Article

Prevalence and Impact of Sarcopenia on Long-Term Mortality in Patients with Peripheral Arterial Disease: An NHANES Longitudinal Study

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SUMMARY

Background: Few studies have examined sarcopenia's impact on peripheral arterial disease (PAD) prognosis. We aimed to investigate the impact of sarcopenia on long-term mortality in community-dwelling patients with PAD.
Methods: Data were extracted from the NHANES 1999–2004. Participants ≥ 40 years old who had PAD defined by ankle-brachial index were eligible. Participants were categorized as having low and normal muscle mass according to body mass index adjusted appendicular lean mass, measured by the dual-energy X-ray absorptiometry. In the NHANES 1999–2002 cycle, knee extensor strength in participants aged ≥ 50 years was measured using a Kin Com MP dynamometer. All-cause and cardiovascular disease (CVD) mortality were compared between the two groups using the Cox proportional hazard analysis.
Results: A total of 623 participants, of which 27.4% had low muscle mass, were included. After adjustment, low muscle mass was significantly associated with an increased risk of all-cause mortality (aHR = 1.31, 95% CI: 1.03–1.65) and CVD mortality (aHR = 1.26, 95% CI: 0.68–2.35) than those without low muscle mass. According to the sub-analyses, low muscle strength alone was not significantly associated with mortality. Reduced muscle mass combined with low muscle strength increased the risk of CVD mortality (aHR = 2.50, 95% CI: 1.12–5.60).
Conclusions: In adults with PAD, low muscle mass elevates the risk of all-cause mortality, while the combination of low muscle mass and reduced muscle strength strongly increases the risk of CVD mortality. These findings underscore the need to assess both muscle mass and strength in the management of PAD.

1. Background

Peripheral arterial disease (PAD) is a relatively common condition in the elderly, and it is estimated that 15% to 20% of persons over 70 years of age have PAD.[1] Its prevalence increases with age, approximately 3% in persons 50 to 59 years of age and 6% in those 60 to 69 years. In persons with PAD, blood flow to the limbs is reduced due to narrowed peripheral arteries, which is primarily due to atherosclerotic occlusive disease of the arteries.[1] Although common, intermittent claudication affects only 10% of PAD patients, while up to 75% are asymptomatic.[2] In 2015, an estimated 240 million people worldwide had PAD, with symptoms ranging from none to severe.[3]

Risk factors for PAD are similar to those for cardiovascular disease (CVD), including diabetes mellitus, hypercholesterolemia, hypertension, reduced kidney function, and smoking.[3] Persons with PAD have a marked increased risk of death from coronary heart disease and cerebrovascular disease.[3,4] Smoking, diabetes, and a low baseline ankle-brachial index (ABI) are risk factors for increased mortality in patients with PAD.[4,5]

Sarcopenia is characterized by critically low levels of muscle mass, muscle strength, and/or muscle performance that predisposes individuals to adverse health outcomes. Older adults with sarcopenia face higher rates of disability, poor quality of life, and death, regardless of age, sex, or comorbidities, compared to those without sarcopenia.[6,7] PAD and sarcopenia frequently coexist, and many PAD patients are diagnosed with sarcopenia, with likely more cases remaining undiagnosed. PAD often leads to systemic muscle loss, reduced strength, and physical decline due to a sedentary lifestyle, decreased mobility, and comorbidities. The relationship between PAD and sarcopenia appears to be bidirectional: advanced vascular aging can negatively affect skeletal muscles, while the loss of muscle mass and strength may further exacerbate cardiovascular risk.[8,9]

While the link between sarcopenia and mortality is established in general populations, few studies have examined sarcopenia's impact on PAD prognosis. Recent studies suggested the link between lower muscle mass and higher mortality in PAD patients.[10,11] The results can help identify high-risk individuals and develop targeted interventions to ultimately lower mortality in PAD patients.

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2. Methods

2.1. Study design

This retrospective study used data from the National Health and Nutrition Examination Survey (NHANES) 1999–2004. NHANES is an ongoing national survey conducted annually in the United States (US), managed by the National Center for Health Statistics (NCHS), which operates under the Centers for Disease Control and Prevention. It assesses the health and nutrition in two-year cycles using a complex sampling design. Data are publicly available, and participants undergo interviews and detailed evaluations at mobile examination centers, including physical exams and lab tests. NHANES data are de-identified, thus additional ethical approval is not required.

2.2. Study population and variables

Participants aged ≥ 40 who underwent ABI assessment, diagnosed with PAD based on abnormal ABI results were eligible. Those lacking complete dual energy X-ray absorptiometry (DEXA) – measured appendicular lean muscle mass (ALM), body mass index (BMI), or mortality data were excluded. We categorized participants into two groups: those with low muscle mass and those with normal muscle mass based on BMI-adjusted ALM (ALM_{BMI}).

2.2.1. Mortality

The NHANES Linked Mortality File links participants to the National Death Index (NDI) to confirm vital status and cause of death. CVD mortality is identified using International Classification of Diseases (ICD) codes from death certificates, capturing deaths from coronary heart disease, heart failure, stroke, and related conditions.

2.2.2. PAD

The most common screening test for PAD is the ABI, defined as the ratio of ankle to brachial systolic blood pressure (SBP).[5] It is frequently used as a marker for PAD in asymptomatic individuals, though its use as a screening tool has been debated.[5] ABI is calculated for each leg by dividing the higher ankle artery pressure by the higher of the two brachial systolic pressures.[12] In a prior study, PAD was defined as an ABI < 0.9 on either side.[13] Severity of PAD was classified into three levels: mild (0.7 ≤ ABI < 0.9), moderate to severe (0.5 ≤ ABI < 0.7), and severe (ABI < 0.5).[13]

2.2.3. Low muscle mass

Body composition was assessed using a DEXA scanner by trained technicians. The DEXA whole-body examination in NHANES measures several important body composition parameters including: total mass, bone mineral content (BMC), bone area, bone mineral density (BMD), fat mass, and lean mass both with and without BMC, and the percentage of body fat. Protocols and procedures in NHANES can be found at the page: https://wwwn.cdc.gov/Nchs/Nhanes/Dxa/Dxa.aspx. Appendicular lean muscle mass (ALM) was calculated by summing the lean mass of the limbs, excluding bone. The FNIH defines sarcopenia as ALM below 19.75 kg in men and 15.02 kg in women. The FNIH also defines low lean muscle mass using ALM divided by BMI (ALM_{BMI}). According to this definition, low lean muscle mass is classified as ALM_{BMI} below 0.789 for men and below 0.512 for women.[14] We used the latter method.

2.2.4. Low muscle strength

In the NHANES 1999–2002 cycle, knee extensor strength in participants aged ≥ 50 was measured using a Kin Com MP dynamometer. Grip strength data was unavailable in the study cycles assessing PAD, so the analysis focused on knee extensor strength. Low muscle strength was defined as knee extensor peak force at or below the 75th percentile of the study population.[15]

2.2.5. Other variables

Extracted NHANES data included demographics, lifestyle factors, and comorbidities. BMI was derived from the NHANES physical examination profiles. Hypertension is defined as an SBP ≥ 140 mmHg, DBP ≥ 90 mmHg (averaged from three measurements), or self-reported diagnosis or use of antihypertensive medication. Diabetes was defined by a doctor's diagnosis, glucose-regulating medication use, or specific glucose/HbA1c levels.[16] Hyperlipidemia was defined as the use of prescribed lipid-lowering medication or a total cholesterol level > 240 mg/dL.[17] CVD was defined as coronary heart disease, angina, myocardial infarction, heart failure, or stroke, while CKD was defined by eGFR using the MDRD equation.[18] The study also examined high-sensitivity C-reactive protein, statin, antiplatelet drug, and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker.

2.3. Statistical analysis

NHANES data were weighted to represent the US population, with sample weights reflecting each participant's representation. Categorical variables are shown as unweighted counts (weighted proportions), and continuous variables as mean (SE). The Wald chi-square test and PROC SURVEYREG examined group differences for categorical and continuous variables. Cox models assessed the impact of low muscle mass on mortality, with further analyses evaluating low muscle strength and the combined effect of both. Variables significant in univariate analysis were adjusted in the multivariable analysis. A $p < 0.05$ was considered significant. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

3. Results

A total of 623 participants were included, representing 5,801,200 US individuals after weighting (Figure 1). The mean age was 67.7 years, with an average follow-up of 113.2 person-months. Low muscle mass was present in 27.4% of participants. Those with low muscle mass had a higher mortality rate (59.02% vs. 40.24%, $p = 0.001$). Significant differences between low and normal muscle mass groups were found in age, race, smoking history, ALM, BMI, and frequencies of hypertension, hyperlipidemia, and CVD (all $p < 0.05$) (Table 1).

3.1. Association between low muscle mass and mortality

Univariate analysis of the variables and low muscle mass is presented in Supplemental Tables S1 and S2. After adjustment, low muscle mass remained significantly associated with an increased all-cause mortality risk (adjusted HR [aHR] = 1.31, 95% CI: 1.03–1.65). Subjects with PAD and low muscle mass did not have a significantly greater risk for CVD mortality (aHR = 1.26, 95% CI: 0.68–2.35) (Table 2).

3.2. Association between low muscle strength and mortality

We further evaluated associations between reduced muscle strength and mortality in a sub-population (aged ≥ 50 from 1999–2002). After adjustment, low muscle strength was not significantly

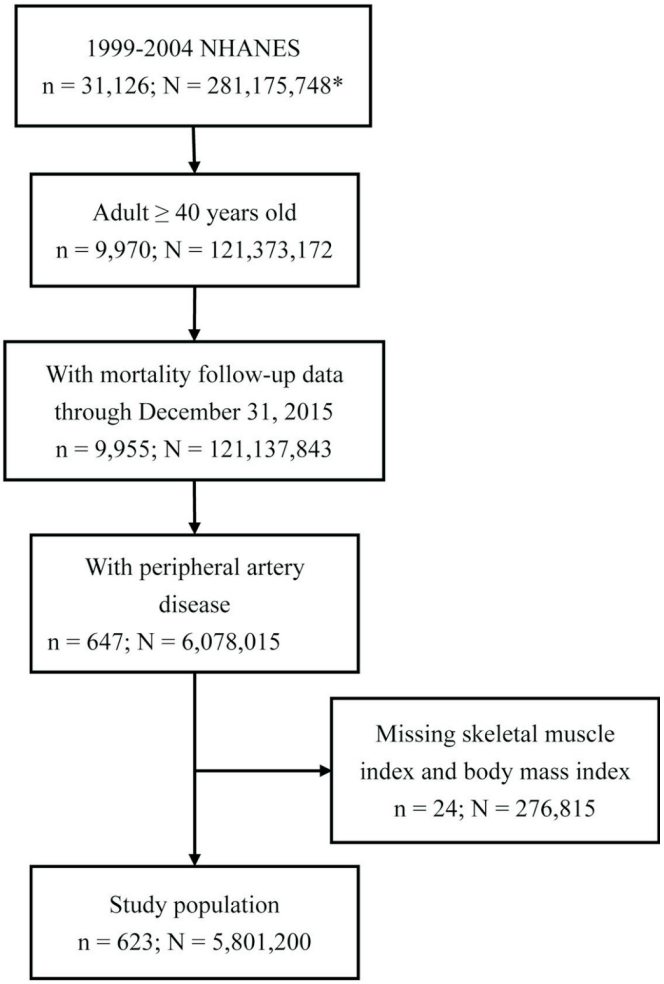

Figure 1. Flow diagram of patient inclusion. * n = actual number of patients; N = the representative sample of the United States population based on the NHANES weighting procedure. NHANES, National Health and Nutrition Examination Survey.

associated with all-cause mortality (aHR = 0.92, 95% CI: 0.63–1.33) and CVD mortality (aHR = 0.97, 95% CI: 0.31–3.04) (Supplementary Table S3).

3.3. Association between combining muscle strength with muscle mass and mortality

Supplemental Table S4 shows that participants with low muscle mass but normal strength had no increased risk of all-cause or CVD mortality. Combined low muscle mass and strength was not associated with higher all-cause mortality risk but had a significantly higher CVD mortality risk (aHR = 2.50, 95% CI: 1.12–5.60) (Supplementary Table S4).

4. Discussion

In our study, 27% of adults with PAD had low muscle mass, which was linked to a 31% higher risk of all-cause mortality but not CVD mortality. Our sub-analysis revealed that reduced muscle strength alone does not show significant impact on mortality. Moreover, patients with low muscle mass but normal strength had no increased mortality risk, whereas those with both low muscle mass and reduced strength had a 2.5-fold higher CVD mortality risk.

In our study, 27% of patients with PAD had low muscle mass, a prevalence that aligns with the rates reported in the literature. Previous studies have documented sarcopenia prevalence in PAD patients ranging from 25% to 35%.[9,19]

There is no consensus on the operational definition of sarcopenia, and one of the most widely used is the 2018 definition proposed by the European Working Group of Sarcopenia in Older People 2 (EWGSOP2).[7] Nevertheless, various tools have been developed to screen for sarcopenia by measuring muscle strength and/or mass.[20]

Decreased muscle mass/muscle wasting has been associated with PAD. Ohori et al. reported links between PAD and low muscle mass in heart failure patients, possibly attributed to reduced physical activity from leg pain, muscle wasting from poor blood flow, and inflammation with oxidative stress.[21] The extent of oxidative damage in the gastrocnemius muscle has been shown to correlate with advanced stages of the disease and reduced muscle fiber cross-sectional area, highlighting the pathological significance of excessive oxidative stress in muscle fiber damage in PAD.[22] Mitochondrial dysfunction, involving disruptions in biogenesis, dynamics, and mitophagy, is a key pathophysiological mechanism in both sarcopenia and PAD.[23] Systemic inflammation, a key factor in the pathophysiology of PAD, may also contribute to skeletal muscle atrophy.[24] This suggests that sarcopenia in PAD patients may originate from alterations in inflammatory processes, potentially mediated by signaling pathways such as the IGF-1/PI3K/Akt/mTOR,[25] the RISK and SAFE,[26] and the TGF β pathways.[27]

PAD patients with sarcopenia or reduced muscle mass/strength have worse outcomes, though varied sarcopenia definitions make comparisons difficult. Sharpe et al.[28] used low muscle mass as a surrogate for sarcopenia, finding that PAD patients with low muscle mass undergoing revascularization had worse postoperative disease progression. Sivaharan et al.[29] found that sarcopenia in PAD patients undergoing lower limb bypass surgery was linked to higher mortality and amputation rates. Our study shows that combined low muscle strength and mass increase cardiovascular mortality risk in PAD patients. However, the link to all-cause mortality was non-significant in sub-analysis, likely due to a smaller sample size.

Endovascular interventions may be preferred over more complex and expensive approaches in PAD, especially given the reduced survival rates in sarcopenic patients.[30] Clinicians should consider incorporating resistance training and nutritional interventions to optimize skeletal muscle mass and potentially improve outcomes. Inflammation control, which can help alleviate both sarcopenia and atherosclerosis, may be another key area for ongoing research.[31] Future therapies for sarcopenia may involve testosterone, anabolic steroids, androgen receptor modulators, beta-blockers, metformin, and ACE inhibitors, all showing potential in management.

Given the strong association between low muscle mass and mortality in PAD patients observed in this analysis, we recommend integrating routine screening for sarcopenia into PAD management protocols. Such screening should include assessments of both muscle mass and strength. Also, clinicians should prioritize early interventions, such as supervised exercise therapy with a focus on resistance training,[32] to enhance muscle strength and prevent further loss. Additionally, tailored nutritional support to optimize muscle protein synthesis — emphasizing adequate intake of protein and essential amino acids[33] — may be incorporated.

4.1. Strengths and limitations

The key strength of this study is its status as the first population-based analysis of sarcopenia's impact on PAD mortality, using DEXA for muscle mass measurement, a gold standard, while also assessing the combined effect of muscle strength and mass. Limita-

Table 1
Characteristics of patients with PAD.

	Total (N = 623)	Low muscle mass		P
		Yes (n = 171)	No (n = 452)	
All-cause mortality	315 (44.59%)	102 (59.02%)	213 (40.24%)	**0.001** [b]
CVD mortality	91 (13.36%)	30 (18.89%)	61 (11.69%)	0.124 [b]
PAD severity by ABI				0.163 [b]
Mild	431 (75.08%)	114 (67.35%)	317 (77.41%)	
Moderate to severe	148 (19.19%)	48 (26.00%)	100 (17.14%)	
Severe	44 (5.73%)	9 (6.65%)	35 (5.45%)	
ALM (kg)	19.63 (0.28)	17.60 (0.48)	20.24 (0.29)	**< 0.001** [a]
BMI (kg/m^2)	28.52 (0.32)	30.02 (0.42)	28.07 (0.38)	**< 0.001** [a]
BMI, categories				**< 0.001** [b]
Normal or below	194 (29.76%)	28 (13.97%)	166 (34.51%)	
Overweight	243 (36.08%)	85 (46.15%)	158 (33.05%)	
Obese	186 (34.16%)	58 (39.88%)	128 (32.43%)	
ALM_{BMI}	0.70 (0.01)	0.59 (0.02)	0.73 (0.01)	**< 0.001** [a]
Age (years)	67.69 (0.63)	73.14 (1.03)	66.05 (0.69)	**< 0.001** [a]
Follow-up duration (person-months)	113.17 (2.74)	117.90 (3.05)	97.48 (5.94)	**0.003** [b]
Sex				0.367 [b]
Male	306 (41.88%)	92 (45.98%)	214 (40.64%)	
Female	317 (58.12%)	79 (54.02%)	238 (59.36%)	
Race/ethnicity				**< 0.001** [b]
Hispanic	117 (6.14%)	60 (11.60%)	57 (4.49%)	
Non-Hispanic White	349 (77.74%)	102 (85.35%)	247 (75.45%)	
Non-Hispanic Black	144 (14.01%)	8 (2.81%)	136 (17.39%)	
Other	13 (2.11%)	1 (0.24%)	12 (2.67%)	
Poverty income ratio				0.494 [b]
Not poor	439 (85.57%)	117 (83.08%)	322 (86.37%)	
Poor	119 (14.43%)	40 (16.92%)	79 (13.63%)	
Missing	65	14	51	
Education				0.455 [b]
High school and above	354 (69.26%)	83 (66.45%)	271 (70.11%)	
< High school	264 (30.74%)	86 (33.55%)	178 (29.89%)	
Missing	5	2	3	
Married/live with partner				0.420 [b]
No	281 (42.08%)	75 (45.46%)	206 (41.04%)	
Yes	322 (57.92%)	91 (54.54%)	231 (58.96%)	
Missing	20	5	15	
Smoking status				**0.035** [b]
Never	210 (34.39%)	53 (31.18%)	157 (34.73%)	
Former	265 (40.31%)	88 (51.76%)	177 (39.16%)	
Current	147 (25.31%)	29 (17.06%)	118 (26.11%)	
Excessive drinking				0.087 [b]
No	433 (86.74%)	120 (91.20%)	313 (85.43%)	
Yes	61 (13.26%)	12 (8.80%)	49 (14.57%)	
Missing	129	39	90	
Sedentary time (hours)				0.852 [b]
< 3	250 (39.61%)	68 (37.55%)	182 (40.22%)	
3-6	364 (59.11%)	100 (61.12%)	264 (58.51%)	
6+	8 (1.28%)	2 (1.33%)	6 (1.27%)	
Missing	1	1	0	
Diabetes				0.061 [b]
No	447 (75.33%)	113 (66.67%)	334 (77.93%)	
Yes	176 (24.67%)	58 (33.33%)	118 (22.07%)	
Hypertension				**0.047** [b]
No	144 (26.28%)	40 (19.43%)	104 (28.35%)	
Yes	479 (73.72%)	131 (80.57%)	348 (71.65%)	
SBP (mm Hg)				0.794 [b]
< 127	157 (27.69%)	44 (27.34%)	113 (27.80%)	
127–140	146 (25.80%)	46 (25.16%)	100 (25.99%)	
141–160	144 (24.58%)	32 (22.03%)	112 (25.36%)	
> 160	150 (21.93%)	42 (25.46%)	108 (20.85%)	
Missing	26	7	19	
Hyperlipidemia				**0.033** [b]
No	278 (40.77%)	73 (33.21%)	205 (43.05%)	
Yes	345 (59.23%)	98 (66.79%)	247 (56.95%)	
CVD				**0.011** [b]
No	412 (66.18%)	107 (54.24%)	305 (69.77%)	
Yes	211 (33.82%)	64 (45.76%)	147 (30.23%)	

Table 1. Continued.

	Total (N = 623)	Low muscle mass		P
		Yes (n = 171)	No (n = 452)	
CKD				0.094 [b]
No	397 (70.18%)	103 (61.81%)	294 (72.76%)	
Yes	182 (29.82%)	56 (38.19%)	126 (27.24%)	
Missing	44	12	32	
hs-CRP (mg/dL)				0.295 [b]
Normal	489 (82.43%)	129 (78.83%)	360 (83.54%)	
Elevated	95 (17.57%)	32 (21.17%)	63 (16.46%)	
Missing	39	10	29	
Average knee extensor peak force (N/m)				**0.014** [b]
Not reduced	57 (26.24%)	8 (10.80%)	49 (30.52%)	
Reduced	172 (73.76%)	47 (89.20%)	125 (69.48%)	
Missing	394	116	278	
Statin use				0.410 [b]
No	452 (69.78%)	120 (66.55%)	332 (70.76%)	
Yes	171 (30.22%)	51 (33.45%)	120 (29.24%)	
Antiplatelet use				0.123 [b]
No	572 (91.55%)	154 (87.66%)	418 (92.72%)	
Yes	51 (8.45%)	17 (12.34%)	34 (7.28%)	
ACEI/ARB use				**0.005** [b]
No	421 (69.08%)	108 (59.25%)	313 (72.05%)	
Yes	202 (30.92%)	63 (40.75%)	139 (27.95%)	

Categorical variables are presented in unweighted counts (weighted proportion), and continuous variables are presented in mean (SE). $p < 0.05$ indicates statistically significant difference between groups. [a] Using proc surveyreg procedure. [b] Using Wald chi-square test.
ABI, ankle-brachial index; ACEI, angiotensin converting enzyme inhibitor; ALM, appendicular lean mass; ARB, angiotensin receptor blockers; BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; PAD, peripheral artery disease; SBP, systolic blood pressure.

Table 2
Associations between low muscle mass (yes vs. no) and mortality in patients with PAD.

Outcomes	aHR (95% CI)
All-cause mortality [a]	1.31 (1.03–1.65)
CVD mortality [b]	1.26 (0.68–2.35)

aHR, adjusted hazard ratio; BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease.
Subjects with missing each laboratory variables were excluded. $p < 0.05$ indicates statistical significance between groups.
[a] Adjusted for variables, including PAD severity, age, sex, BMI in categories, race, smoking, diabetes, hypertension, SBP, CVD, and CKD.
[b] Adjusted for variables, including PAD severity, age, sex, BMI in categories, married/live with partner, hypertension, and CKD.

tions include potential recall bias from NHANES data, the use of BMI-adjusted ALM and knee extensor strength, which may not fully capture sarcopenia's complexity, and the absence of grip strength data. Lastly, ABI measurements may misclassify PAD in older adults due to arterial stiffness, and small sample sizes in sub-analyses may have reduced statistical power.

5. Conclusion

This study found that about 27% of US adults aged 40+ with PAD have low lean muscle mass, which is independently linked to a 31% higher risk of all-cause mortality, but not CVD mortality. However, when combined with reduced muscle strength, there's a strong association with increased CVD mortality, underscoring the importance of comprehensive sarcopenia screening in PAD management.

Availability of data and materials

All data are included in the manuscript and its supplemental files.

Competing interests

The authors declare no competing interests.

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Authors' contributions

Wei Ho: Conception; Drafting manuscript. Fan-Yen Lee: Analysis and interpretation of data; Critical revision. Kwan-Ru Huang: Analysis and interpretation of data; Critical revision. Yu Lun Chou: Acquisition of data; Critical revision. Hsu-Ting Yen: Acquisition of data; Critical revision. I Cheng Liu: Analysis and interpretation of data; Critical revision. Chun Hsiang Yang: Analysis and interpretation of data; Critical revision. Jiunn Jye Sheu: Analysis and interpretation of data; guarantor of integrity; Supervision.

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Supplementary materials

Supplementary materials for this article can be found at http://www.sgecm.org.tw/ijge/journal/view.asp?id=34.

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