RESEARCH ARTICLE

WILEY

Prevalence and correlative factors of hyperhomocysteinemia in elderly patients with femoral neck fracture: A cross-sectional study

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Abstract

Aims: The occurrence of hyperhomocysteinemia (HHcy) in elderly patients with femoral neck fracture (FNF) draws little attention from surgeons preoperatively. The aim of our study was to determine the prevalence and correlative factors of HHcy in elderly patients (≥65 years) with FNF prior to surgery.

Methods: We retrospectively investigated 286 elderly FNF patients aged 65–98 years admitted to our institution from September 2020 to September 2021. Categorical variables were compared using the Chi-squared test, and continuous variables were compared using the Mann–Whitney U test. Univariable and multivariable logistic regression were used to determine the associations of variables with the odds of HHcy.

Results: Among the 286 elderly FNF patients, the prevalence of HHcy was 30.77% and the mean Hcy level was $14.52 \pm 10.49 \, \mu mol/L$. The mean Hcy level and the prevalence of HHcy in male patients were significantly higher than that in female patients ($16.41 \pm 9.58 \, \mu mol/L$ vs. $14.00 \pm 10.69 \, \mu mol/L$, $p = 0.002$; 43.55% vs. 27.23%, $p = 0.014$). Multivariate analysis indicated that being male patient (OR 2.187, 95% CI 1.187–4.028, $p = 0.012$), hypertension (OR 1.993, 95% CI 1.141–3.479, $p = 0.015$), and low HDL-C (OR 2.979, 95% CI 1.353–6.558, $p = 0.007$) were significant correlative factors of HHcy among elderly FNF patients.

Conclusions: This study found a high prevalence of HHcy in elderly FNF patients, with being male patient, hypertension, and low levels of HDL-C as the significant correlative factors after adjusting for age and other covariables. However, further large-scale studies in wider regions are warranted to confirm these findings.

KEYWORDS
elderly, femoral neck fracture, homocysteine, regression model

1 | INTRODUCTION

Studies have reported a dramatically increase in the age-specific incidence of hip fracture in elderly Chinese individuals during the last decade,[1] which brings about a tremendous burden on the public health system of China. Femoral neck facture (FNF), accounting for one-third of all hip fractures, carries a significant risk of morbidity and mortality.[2] Surgical options for FNF in the elderly people could

be hemiarthroplasty or total hip arthroplasty, depending on the bone quality, medical comorbidities, and functional demand of patients.[3]

On the contrary, the treatment effect of FNF does not only depend on the ideal surgical option, but also on the patient's preoperative medical conditions and postoperative rehabilitation. Elderly patients with FNF usually have more and varied comorbidities.[4,5] A recent study indicated that comorbidity is the best predictor of mortality and mobility after hip fracture, after taking into account age, gender, fracture pattern, surgical delay, previous fracture, and comorbidity.[6] Besides, it has been well acknowledged that modifiable risk factors (MRFs) such as obesity, diabetes, tobacco use, anemia, low serum albumin, and poor dentition should be addressed prior to arthroplasty to reduce the incidence of postoperative complications.[7]

Homocysteine (Hcy) is an intermediate amino acid formed during methionine metabolism. Multiple factors such as age, genetics, and lifestyle affect the serum levels of Hcy.[8] Normal serum Hcy levels range from 5 to 15 μmol/L in the fasting state. Elevated levels of serum homocysteine (>15 μmol/L), termed hyperhomocysteinemia (HHcy), has been considered as a trigger for a variety of diseases, such as Alzheimer's disease, atherosclerosis, venous thromboembolism, congestive heart failure, age-related macular degeneration, hearing loss, and even cancers.[9–11] For these reasons, clinicians should strive to detect HHcy in their patients and provide timely treatment. Study has shown that the levels of serum Hcy can easily and safely be corrected with supplementation of folic acid or B vitamins, regardless of the cause.[12]

Although HHcy has been a well-established risk factor for many cardiovascular and cerebrovascular diseases, the occurrence of HHcy in elderly FNF patients draws little attention from surgeons prior to arthroplasty, not to mention the preoperative addressing. In our study, we investigated the prevalence and correlative factors of HHcy in elderly patients (≥65 years) with FNF prior to arthroplasty, aiming to provide information that may improve the preoperative assessment and optimization of elderly FNF patients in the future clinical practices.

2 | MATERIALS AND METHODS

This study was approved by the local Hospital Ethical Committee. Informed consent was waived due to the retrospective design of the study. Between September 2020 and September 2021, elderly patients (≥65 years) with FNF admitted to our institution (a tertiary hospital) were retrospectively investigated. Cases of pathologic fracture caused by neoplasms were not included in this study. Cases on lipid-lowering drugs, vitamin B12, and folic acid were also excluded. Finally, a total of 286 FNF patients between 65 and 98 years were included in this study.

Patients were evaluated regarding age, gender, body mass index (BMI), drinking status, smoking status, arterial hypertension, diabetes, dyslipidemia, and serum homocysteine levels. The BMI was calculated as weight in kilograms divided by the square of the

height in meters. Arterial hypertension was defined as systolic blood pressure greater than 140 mm Hg, diastolic blood pressure of 90 mmHg or greater, or the need for antihypertensive drugs to maintain blood pressure within normal limits. Diabetes was defined as fasting plasma glucose ≥7 mmol/L (126 mg/dL) and/or being on treatment for diabetes. Current drinking was defined as alcohol consumption of ≥8 g/week. Current smoking was defined as people who smoked at least one cigarette every day and continued for at least 1 year.

Fasting blood samples were collected in the morning after at least 10 h of fasting for all subjects. Serum Hcy level was measured by enzyme cycling method on the Hitachi 912 automatic chemistry analyzer (Hitachi, Japan). HHcy was defined as serum total Hcy of >15 μmol/L according to previously published reports. Serum lipid profiles were measured by enzymatic method using the Dimension analyzer (Siemens). High triglycerides (TG) was defined as triglycerides of ≥1.7 mmol/L. High total cholesterol (TC) was defined as total cholesterol of ≥5.2 mmol/L. High low-density lipoprotein cholesterol (LDL-C) was defined as low-density lipoprotein cholesterol of ≥3.12 mmol/L. Low high-density lipoprotein cholesterol was defined as high-density lipoprotein cholesterol (HDL-C) of <1.04 mmol/L.

Descriptive statistics were calculated for all the variables, including continuous variables (reported as mean values ± standard deviations) and categorical variables (reported as numbers and percentages). Continuous variables were compared using the Mann–Whitney U test. Categorical variables were compared using the Chi-squared test. Variables with statistical significance in the univariate analysis were included in the multivariate logistic regression with the forward stepwise method of variable selection. To measure the magnitude of the effect, odds ratio (OR) and 95% confidence interval (CI) were calculated. A p-value of <0.05 indicated statistical significance. All statistical analyses were performed using SPSS 19.0 software (SPSS Inc).

3 | RESULTS

The baseline characteristics of the included patients are shown in Table 1. In total, 286 FNF patients aged 65–98 years were included. Their mean age was 77.78 ± 7.91 years. The majority of patients were female patients ($n = 224$, 78.32%). For the whole population, the prevalence of HHcy was 30.77% (88 of 286). The mean serum Hcy levels was 14.52 ± 10.49 μmol/L, ranging from 4.5 to 106.2 μmol/L.

The mean Hcy levels and the prevalence of HHcy in male patients were significantly higher than that in female patients (16.41 ± 9.58 μmol/L vs. 14.00 ± 10.69 μmol/L, $p = 0.002$; 43.55% vs. 27.23%, $p = 0.014$). Besides, male patients presented significantly older mean age (78.18 ± 7.85 years vs. 77.67 ± 7.94 years, $p = 0.006$), and higher percentages of current smoking (33.87% vs. 0.89%, $p = 0.000$) and current drinking (25.81% vs. 3.13%, $p = 0.000$) compared with female patients. However, the mean levels of TC (4.83 ± 0.98 mmol/L vs. 4.50 ± 1.02 mmol/L, $p = 0.019$) and LDL-C (2.76 ± 0.73 mmol/L vs. 2.48 ± 0.72 mmol/L, $p = 0.006$), and the

TABLE 1 Baseline characteristics of the 286 patients with femoral neck fracture (FNF)

Variables	Overall (n = 286) Mean ± SD or n (%)	Female (n = 224) Mean ± SD or n (%)	Male (n = 62) Mean ± SD or n (%)	p value
Age (years)	77.78 ± 7.91	77.67 ± 7.94	78.18 ± 7.85	**0.006**[*]
65–69	57 (19.93%)	44 (19.64%)	13 (20.97%)	0.380
70–74	53 (18.53%)	46 (20.54%)	7 (11.29%)	
75–79	56 (19.58%)	42 (18.75%)	14 (22.58%)	
80–85	50 (17.48%)	35 (15.63%)	15 (24.19%)	
85–89	51 (17.83%)	42 (18.75%)	9 (14.52%)	
≥90	19 (6.64%)	15 (6.70%)	4 (6.45%)	
Hypertension	165 (57.69%)	134 (59.82%)	31 (50.00%)	0.166
Diabetes	46 (16.08%)	42 (18.75%)	4 (6.45%)	**0.020**[*]
Current smoking	23 (8.04%)	2 (0.89%)	21 (33.87%)	**0.000**[*]
Current drinking	23 (8.04%)	7 (3.13%)	16 (25.81%)	**0.000**[*]
BMI	21.13 ± 3.18	21.09 ± 3.26	21.30 ± 2.91	0.490
<25	258 (90.21%)	202 (90.18%)	56 (90.32%)	0.973
≥25	28 (9.79%)	22 (9.82%)	6 (9.68%)	
TG level (mmol/L)	1.24 ± 0.83	1.27 ± 0.88	1.13 ± 0.64	0.225
High TG	46 (16.08%)	37 (16.52%)	9 (14.52%)	0.704
TC level (mmol/L)	4.76 ± 1.00	4.83 ± 0.98	4.50 ± 1.02	**0.019**[*]
High TC	87 (30.42%)	71 (31.70%)	16 (25.81%)	0.372
LDL-C level (mmol/L)	2.70 ± 0.73	2.76 ± 0.73	2.48 ± 0.72	**0.006**[*]
High LDL-C	72 (25.17%)	61 (27.23%)	11 (17.74%)	0.128
HDL-C level (mmol/L)	1.41 ± 0.32	1.41 ± 0.32	1.40 ± 0.33	0.901
Low HDL-C	32 (11.19%)	22 (9.82%)	10 (16.13%)	0.163
Hcy level (μmol/L)	14.52 ± 10.49	14.00 ± 10.69	16.41 ± 9.58	**0.002**[*]
HHcy	88 (30.77%)	61 (27.23%)	27 (43.55%)	**0.014**[*]

[*]p < 0.05 between groups.

percentage of diabetes (18.75% vs. 6.45%, p = 0.020) were significantly higher in female patients compared to male patients.

Univariate analysis showed significant associations between HHcy and gender, hypertension, current drinking, and low HDL-C, as shown in Table 2. Multivariate analysis indicated that being male patient (OR 2.187, 95% CI 1.187–4.028, p = 0.012), hypertension (OR 1.993, 95% CI 1.141–3.479, p = 0.015), and low HDL-C (OR 2.979, 95% CI 1.353–6.558, p = 0.007) were the three significant correlates of HHcy in FNF patients, as shown in Table 3. The fit of the multivariate regression model was tested with the Hosmer–Lemeshow test (p = 0.183) and the overall correctly classified percentage was 72.0%.

4 | DISCUSSION

A number of factors, such as sarcopenia, osteoporosis, poor vision, neurological or cognitive impairment, and malnutrition, contribute to the high incidence of FNF in elderly populations.[3,13] A total of

286 elderly patients (≥65 years) with FNF were included in our current study. Among them, female patients constituted the majority (78.32%). It is generally acknowledged that female patients have a much higher incidence of hip fracture than male patients, which may be attributed to the decline in estrogen secretion and osteoporosis in postmenopausal women.[14,15] We also found that mean age in male FNF patients was slightly older than that in female FNF patients (78.18 ± 7.85 years vs. 77.67 ± 7.94 years, p = 0.006), which is in line with the point that men who have a hip fracture are more often biologically older and chronically ill than their female counterparts.[16,17]

As mentioned above, elderly FNF patients are usually complicated with various frailties or comorbidities, so preoperative risk assessment in those patients is of particular importance. Evidence suggests that preoperative optimization of MRFs reduce the incidence of complications such as infection, prosthetic loosening, and fracture following hip or knee arthroplasty.[18] A growing number of studies have established that HHcy is correlated with multiple disorders or pathological processes such as neurodegeneration, venous thromboembolism, hypertension, inflammatory bowel disease,

TABLE 2 Correlative factors of HHcy in elderly FNF patients by univariate analysis

Variables	HHcy (n = 88) Mean ± SD or n (%)	Non-HHcy (n = 198) Mean ± SD or n (%)	p value
Age(years)	77.57 ± 8.03	77.88 ± 7.87	0.762
>65, ≤80 years	53 (60.23%)	113 (57.07%)	0.618
>80 years	35 (39.78%)	85 (42.93%)	
Gender (Male)	27 (30.68%)	35 (17.68%)	0.014*
Hypertension	59 (67.05%)	106 (53.54%)	0.033*
Diabetes	14 (15.91%)	32 (16.16%)	0.957
Current smoking	10 (11.36%)	13 (6.57%)	0.168
Current drinking	12 (13.64%)	11 (5.56%)	0.020*
BMI	20.78 ± 2.88	21.30 ± 3.30	0.148
<25	80 (90.91%)	178 (89.90%)	0.791
≥25	8 (9.09%)	20 (10.10%)	
TG level (mmol/L)	1.32 ± 0.93	1.20 ± 0.79	0.290
High TG	15 (17.05%)	31 (15.66%)	0.768
TC level (mmol/L)	4.69 ± 1.03	4.79 ± 0.98	0.526
High TC	26 (29.55%)	61 (30.81%)	0.830
LDL-C level (mmol/L)	2.67 ± 0.73	2.71 ± 0.73	0.776
High LDL-C	24 (27.27%)	48 (24.24%)	0.586
HDL-C level (mmol/L)	1.37 ± 0.35	1.43 ± 0.31	0.218
Low HDL-C	17 (19.32%)	15 (7.58%)	0.004*

*p < 0.05 between groups.

TABLE 3 Correlative factors of HHcy in elderly FNF patients by multivariate analysis

Variables	Odds ratio	95% confidence interval	p value
Being male	2.187	1.187–4.028	0.012*
Hypertension	1.993	1.141–3.479	0.015*
Low HDL-C	2.979	1.353–6.558	0.007*

*p < 0.05 between groups.

osteoporotic fracture, and cardiovascular disease.[9–11,19–21] As reported by Lim et al. in 2004, the prevalence of HHcy among their 104 elderly patients (aged >55 years) with hip fracture was as high as 52.3%.[22] Except for that, little attention has been given to the prevalence of HHcy in elderly patients with FNF in recent years.

The reported prevalence of HHcy varied among populations residing in different regions. Based on a survey data from 2001 to 2006, Li et al. found the prevalence of HHcy was 6.87% among 9331 US adult populations (aged ≥20 years).[23] de Bree et al revealed in 2005 that the prevalence of HHcy was 10.9% among 25,489 European

adult populations (aged ≥20 years).[24] A recent meta-analysis by Yang et al. showed that the pooled prevalence of HHcy was 27.5% among 60,754 Chinese populations aged 3–97 years.[25] To the best of our knowledge, this seems the first study to investigate the prevalence and correlative factors of HHcy in elderly FNF patients preoperatively. The results showed that, among the 286 FNF patients aged 65–98 years, the prevalence of HHcy was 30.77%. We considered that the reasons for the relative higher prevalence of HHcy in this study might be the older age of included cases. Several possible mechanisms for the high Hcy levels in elderly populations have been postulated, alternation of renal function, impaired renal metabolism of Hcy, and decreases in vitamin levels might be involved.[26,27]

Consistent with observations from previous studies, our findings revealed that the mean Hcy levels and the prevalence of HHcy in male FNF patients were significantly higher than that in female FNF patients (16.41 ± 9.58 μmol/L vs. 14.00 ± 10.69 μmol/L, $p = 0.002$; 43.55% vs. 27.23%, $p = 0.014$). Several factors might be associated with the increased Hcy levels in males, such as muscle mass, estrogen status, vitamin levels, and life styles. It is well recognized that Hcy production is related to creatine-creatinine synthesis. Male patients usually have a greater need for creatine synthesis as they have more muscle mass, resulting in more Hcy production.[28] Bednarek-Tupikowska et al. revealed that Hcy levels increased with natural menopause and decreased with menopausal hormone replacement therapy, suggesting a close relationship between estrogen status and Hcy levels.[29] Besides, our results revealed that, compared to female FNF patients, male FNF patients had a higher percentage of smoking (33.87% vs. 0.89%, $p = 0.000$) and drinking (25.81% vs. 3.13%, $p = 0.000$), which both have been positively associated with Hcy levels.[30,31]

Based on the multivariate analysis performed in this study, in addition to being male patient, hypertension, and low levels of HDL-C were the two other risk factors for HHcy in elderly FNF patients. Studies have identified that HHcy is positively correlated with the development of hypertension.[20,32,33] Qin et al. reported that hypertension associated with HHcy accounted for approximately 75% of adult hypertensive patients in China.[34] Many HHcy-induced biochemical changes such as increased free radicals, reduced NO bioavailability, and endoplasmic reticulum stress can lead to the damage and dysfunction of endothelium, which play an important role in the pathogenesis of hypertension.[35] On the contrary, many authors held the opinion that HHcy might be the consequence of hypertension. They considered that all patients with hypertension would sooner or later develop endothelium damage resulting from wall shear stress and proatherogenic processes, which might lead to the excessive release of Hcy particles from endothelium cells into blood.[36] So far, the crucial question that whether Hcy is directly involved in the pathogenesis of hypertension or just a marker for increased risk has yet to be clarified.

HDL-C is a cholesterol-rich particle which has been inversely correlated with the risk of atherosclerotic cardiovascular diseases (CVDs) in populations.[37] HDL-C may exert the cardio-protective effect by transporting excess cholesterol from peripheral cells back to

the liver for removal, reducing the oxidation of LDL, and ameliorating endothelial dysfunction.[38] Furthermore, some epidemiological studies have demonstrated the negative influence of HHcy on HDL-C metabolism.[39,40] Guéant-Rodriguez et al. reported in 2011 that Hcy inversely correlated with ApoA-I (apolipoprotein A-I) and with HDL-C among ambulatory elderly populations between 60 and 85 years.[41] ApoA-I is a key structural and functional component of HDL biosynthesis. Liao et al. demonstrated in their experimental study that HHcy reduced circulating HDL-C particles by inhibiting ApoA-I protein synthesis/secretion and enhancing HDL-C clearance.[42] Similar to previous studies, our current study also found that low levels of HDL-C positively correlated with the incidence of HHcy among elderly patients with FNF. Taken together, current studies investigating the relationship between HHcy and HDL-C may contribute to elucidating the mechanisms underlying HHcy-induced diseases.

There were several limitations to the current study. First, given this was a cross-sectional study, we could only probe the correlative factors for HHcy among elderly FNF patients and could not draw conclusions regarding causality. Second, our patients were from a single tertiary hospital, which limits the generalizability of the findings. Lastly, only a limited number of possible correlative factors were included for analysis, and some well-proven correlates of HHcy, such as levels of B vitamins, serum creatinine, and ApoA-I, were not able to be assessed because of the availability of information.

In summary, the present study found a high prevalence of HHcy in elderly FNF patients, with being male patient, hypertension, and low levels of HDL-C as the significant correlative factors after adjusting for age and other covariables. These findings would help the preoperative screening and addressing of HHcy in elderly FNF patients in future clinical practices. However, further large-scale studies in wider regions are warranted to confirm these findings.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this published article.

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