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Two-year morbidity and mortality in elderly patients with syncope

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Abstract

Background: syncope is a common cause of hospitalisation in the elderly. However, morbidity and mortality in elderly patients with syncope is not well established.

Methods: two-hundred and forty-two patients older than 65 years consecutively referred to the participating centres for evaluation of transient loss of consciousness were enrolled in a multicentre 2-year longitudinal observational study. Mortality and syncope recurrences were recorded and multidimensionally evaluated at 6, 12, 18 and 24 months.
Findings: at 24 months, total mortality was 17.2% and syncope recurrence was 32.5%. Cardiac syncope was more frequent in deceased than in survivor patients (21.7 versus 12.3%; $P = 0.03$), whereas neuro-mediated (62.1 versus 66.2%; $P = 0.357$) and unexplained syncope (10.8 versus 11.8%; $P = 0.397$) did not differ between the two groups. Drug-induced and/or multifactorial syncope was less frequent in patients with syncope recurrence (5.7 versus 10.7%; $P = 0.02$). Kaplan–Meyer curves indicated that mortality and syncope recurrence increased significantly with age ($P = 0.006$ and $P = 0.008$, respectively). At multivariate analysis, mortality was significantly predicted by age and comorbidity (hazard ratios: 1.17 and 1.39, and 95% confidence interval 1.01–1.37 and 1.01–1.93, respectively), and syncope recurrence by age and disability (hazard ratio: 1.13 and 1.04, 95% confidence interval 1.01–1.25 and 1.04–2.25, respectively). Depression increased from baseline to the end of follow-up (from 28.3 to 41.4%; $P = 0.001$).
Conclusions: in our patients, mortality was related to increasing age and comorbidity, whereas recurrence was related to increasing age and disability. Cardiac syncope was more frequent in deceased than in survivor patients, and syncope recurrence was high despite a low incidence of unexplained syncope.

Keywords: *elderly, syncope, mortality*

Introduction

Syncope in the elderly is a relevant problem in clinical practice, particularly in geriatric departments [1, 2]. This is in line with the finding that the incidence of syncope increases with age [3]. In a recent Italian study, the median age of patients referred to the emergency department for syncope was 71 years [4]. Similarly, in a cross-sectional study of syncope patients identified from the USA National Inpatient Sample (NIS) database for the years 2000–05, the mean age was 69 years and only 7.7% of patients below the age of 40 suffered from syncope [5].

Despite the high incidence of syncope in older patients, very few studies have prospectively evaluated morbidity and mortality in elderly patients with syncope. Syncope recurrence in the elderly varies between 25 and 30% depending on the setting [6–8]. In contrast, mortality data of elderly patients with syncope differ among studies. In 1986, Kapoor *et al.* found a 2-year overall mortality of 30% in elderly patients versus 9% in young patients with syncope [9]. Thirteen years later, Getchell *et al.* reported a mortality rate of 50% in subjects with syncope aged ≥70 years versus 9% in those aged <70 years [7]. In patients with a main diagnosis of syncope identified from the USA NIS data sets for the years 2000–05, mortality rates progressively increased from the 6th to the 10th decade of life [5]. More recently, Roussanov *et al.* observed that the mortality rate in three age groups (middle age, older and elderly) was similar to that recorded in the general population after adjustment for age and comorbidities (8%) [8].

The aim of this prospective multicentre study was to define the 2-year morbidity and mortality in elderly patients referred to geriatric departments after syncope. Disability, depression, falls and fractures were also investigated.

Methods

Two-hundred and forty-two patients above 65 years of age were enrolled in this study, which was conducted by the Italian Group for the Study of Syncope in the Elderly (GIS), between June 2002 and March 2004 [10]. The patients had been consecutively referred to one of the participating centres for evaluation of a transient loss of consciousness [10]. Eleven patients were excluded because, despite syncope-like symptoms, they did not suffer from syncope and 16 of the remaining 231 patients with syncope dropped out during follow-up (7%). Exclusion criteria were symptoms limited to pre-syncope (a condition in which patients feel that syncope is imminent), severe cognitive impairment [Mini-Mental State Examination (MMSE) score ≤14] [11], active (<5 years) malignancies and disability in more than four activities of daily living [12]. All these conditions are well known to significantly influence follow-up by increasing the number of drop-out patients. Written, informed consent to participate in the follow-up study was obtained in all cases. Subsequently, all medical records were sent to the coordination Center (Florence, Italy) for data analysis.

Diagnostic protocol

Briefly, all patients enrolled in the GIS study were evaluated with the GIS diagnostic algorithm [10]. Syncope was defined as 'neuro-mediated', 'cardiac', 'drug-induced', 'multifactorial' and 'unexplained'. Owing to the limited number of multifactorial and drug-induced syncopes, these two types of syncope were classified collectively as 'other'. Cardiogenic syncope was considered 'mechanical' when it was associated with acute myocardial ischaemia or severe intracardiac flow obstruction (e.g. aortic stenosis, left atrial myxoma or thrombus), and 'arrhythmic' in the presence

one of the following: sinus bradycardia (<40 b.p.m.); recurrent sino-atrial block with pause sec; second- (Mobitz II) or third-degree atrioventricular block; alternating left and right bundle branch block; paroxysmal supraventricular or ventricular tachycardia and pacemaker malfunction. Neuro-mediated syncope was defined: (i) 'vasovagal' when precipitating events such as pain, emotional distress or prolonged standing were associated with typical prodromic symptoms or when the loss of consciousness was induced during the tilt test; (ii) 'situational' when syncope occurred during or immediately after, micturition, defecation, cough or swallowing; (iii) 'carotid sinus syndrome' when carotid sinus massage in the supine or upright position induced syncope with bradycardia or hypotension; (iv) 'orthostatic' when syncope or pre-syncope was associated with a decrease in systolic blood pressure ≤20 mmHg and in diastolic BP ≤10 mmHg within 3 min of standing.

Follow-up

All enrolled participants were followed up until death or follow-up closure. Clinical or telephone follow-up was conducted at 6, 12, 18 and 24 months. During each follow-up, vital status, syncope recurrence, hospitalisation and date of death, if known, were recorded. The MMSE [11], basic activity daily living (BADL) [12] and instrumental activity daily living [13] activities of daily living, and Geriatric Depression Scale (GDS) [14] were also administered. A patient was considered depressed if the GDS score was ≥6.

Statistical analysis

Statistical analysis was carried out with the SPSS software package, version 13.0. Normally distributed data are presented as mean ± standard deviation of the mean. Elderly patients were stratified in age quartiles (65–69, 70–79, 80–89 and ≥90 years old). Student's *t*-test and the χ^2 test were used to compare continuous variables and proportions, respectively. Survival and syncope recurrence were evaluated in a Kaplan–Meyer model. Cox analysis of mortality and syncope recurrence was performed with age, sex, number of drugs assumed, cumulative illness rating scale (CIRS), BADL and IADL lost, MMSE, GDS and type of syncope as covariates, and with the time of the first recurrence as a time-dependent covariate. Clinical variables were subsequently entered stepwise in the model. The assumption of proportionality was checked by visual inspection of the survival curves. A two-tailed $P < 0.05$ was considered statistically significant.

Results

Demographic and clinical characteristics

In the longitudinal GIS study, we evaluated 215 of the 242 elderly patients recruited in the enrolment phase of the study [10]. The main demographic and clinical characteristics of the whole sample and the sample stratified by age are shown in Table 1. Cormorbidity and polypharmacy were high in all patients, whereas the body mass index (BMI) and MMSE score were lowest, and the number of drugs and the prevalence of BADL and IADL lost were highest in the oldest quartile (≥90 years). Interestingly, the number of hospitalisations decreased with increasing age (Table 1).

Baseline age, number of drugs assumed and comorbidity were significantly higher, and baseline BMI and MMSE significantly lower in deceased patients than in survivors (Table 2). Syncope recurred in 70 patients (32.5%). Baseline disability was greater and baseline MMSE slightly lower in these patients. The number of hospitalisations was lower in deceased patients than in either survivors or patients with syncope recurrence (Table 2).

Table 1. Main demographic and clinical characteristics in the whole series and by stratified for age

Variables	All (*n* = 215)	65–69 years (*n* = 25)	70–79 years (*n* = 90)	80–89 years (*n* = 86)	≥90 years (*n* = 14)	*P* for trend
Age (years)	78.7 ± 6.8	67.0 ± 1.3	75.1 ± 2.4	83.1 ± 2.7	92.0 ± 2.6	<0.001
Female (*n*, %)	124 (57.7)	17 (68.0)	48 (53.3)	52 (60.5)	7 (50.0)	0.494 (NS)
BMI (kg/m^2)	25.0 ± 3.4	26.2 ± 4.4	25.6 ± 3.7	24.2 ± 2.7	24.5 ± 2.2	<0.005
Drugs (*n*)	3.4 ± 2.2	2.2 ± 2.3	3.4 ± 2.2	3.6 ± 2.2	6.5 ± 3.8	0.009
CIRS (*n*)	7.2 ± 3.4	5.6 ± 2.9	7.4 ± 3.6	7.4 ± 3.1	6.5 ± 3.8	0.426 (NS)
BADL lost (*n*)	0.6 ± 1.0	0.2 ± 0.4	0.5 ± 0.9	0.6 ± 1.0	0.9 ± 0.9	0.025
IADL lost (*n*)	1.8 ± 3.0	0.0 ± 0.2	1.4 ± 2.7	2.2 ± 3.1	3.7 ± 4.3	<0.001
MMSE (*n*)	26.9 ± 3.8	29.4 ± 0.8	27.6 ± 2.8	25.6 ± 4.6	23.9 ± 3.9	<0.001
GDS (*n*)	3.7 ± 3.6	3.1 ± 3.7	4.0 ± 3.8	3.7 ± 3.6	3.1 ± 1.4	0.680 (NS)
Falls (*n*, %)	137 (63.7)	20 (80.0)	57 (63.3)	51 (59.3)	9 (64.3)	0.469 (NS)
Fractures (*n*, %)	24 (11.1)	3 (15.8)	9 (16.1)	9 (17.0)	3 (33.3)	0.420 (NS)
Hospitalisations (*n*, %)	79 (36.7)	12 (46.1)	35 (39.3)	28 (32.6)	4 (5.1)	0.023
Mortality (*n*, %)	38 (17.7)	0 (0)	13 (14,.4)	19 (22.1)	6 (42.9)	0.006
Syncope recurrence (*n*, %)	70 (32.6)	7 (27.7)	25 (27.8)	32 (37.0)	6(42.8)	0.008

BMI, body mass index; CIRS, Cumulative Illness Rating Scale; BADL, basic activity daily living; IADL, instrumental activity daily living; MMSE, Mini-Mental State Examination; GDS, Geriatric Depression Scale.

Table 2. Main demographic and clinical characteristics stratified by mortality and syncope recurrence

Variables	Death		*P*-value	Syncope recurrence		*P*-value
	Yes ($n = 37$)	No ($n = 178$)		Yes ($n = 70$)	No ($n = 145$)	
Age (years)	83 ± 5	77 ± 7	<0.001	77 ± 6	77 ± 6	0.356 (NS)
Female (*n*, %)	18 (48.6)	106 (59.5)	0.07 (NS)	39 (55.7)	85 (58.6)	0.749 (NS)
BMI (kg/m^2)	23.4 ± 3.0	25.4 ± 3.4	0.02	25.2 ± 2.7	25.6 ± 3.7	0.386 (NS)
Drugs (*n*)	4.2 ± 2.2	3.2 ± 2.2	<0.01	3.2 ± 2.2	3.4 ± 2.3	0.634 (NS)
CIRS (*n*)	9.1 ± 3.1	6.7 ± 3.3	<0.001	7.0 ± 2.8	6.5 ± 3.3	0.704 (NS)
BADL lost (*n*)	0.7 ± 0.8	0.5 ± 1.0	0.399 (NS)	0.8 ± 1.2	0.3 ± 0.8	<0.01
IADL lost (*n*)	2.6 ± 2.7	1.7 ± 2.9	0.198 (NS)	2.3 ± 3.6	1.0 ± 2.5	0.042
MMSE (*n*)	25.1 ± 4.0	27.2 ± 3.7	0.007	26.0 ± 4.0	27.7 ± 2.8	<0.01
GDS (*n*)	2.8 ± 2.3	3.8 ± 3.8	0.163 (NS)	3.8 ± 4.2	3.8 ± 3.6	0.265 (NS)
Falls (*n*, %)	22 (59.4)	115 (64.6)	0.926 (NS)	46 (65.7)	92 (63.4)	0.688 (NS)
Fractures (*n*, %)	10 (27.0)	27 (15.1)	0.233 (NS)	13 (18.5)	20 (13.7)	0.596 (NS)
Hospitalisations	8 (21.6)	71 (39.8)	<0.001	24 (34.2)	55 (37.9)	<0.01

BMI, body mass index; CIRS, Cumulative Illness Rating Scale; BADL, basic activity daily living; IADL, instrumental activity daily living; MMSE, Mini-Mental State Examination; GDS, Geriatric Depression Scale.

Type of syncopes

In our patients, cardiac syncopes accounted for 14% ($n = 30$), neuro-mediated syncopes for 65.6% ($n = 141$), drug-induced and/or multifactorial syncopes ('other') for 8.8% ($n = 19$) and unexplained syncopes for 11.6% ($n = 25$).Overall, the 2-year mortality among patients was 17.2 % (37/215 patients). Cardiac syncope was more frequent in deceased patients than in survivors (21.7 versus 12.3%, $P = 0.03$), whereas neuro-mediated and unexplained syncope did not differ between the two groups. In addition, drug-induced and/or multifactorial syncope was less frequent in patients with syncope recurrence than in patients without syncope recurrence (5.7 versus 10.7, $P = 0.02$). Of the 16 patients who dropped out, syncope was neuro-mediated in 12 (75.0%), cardiac in 3 (18.7%) and unexplained in 1 patient (6.3%).

Mortality and syncope recurrence

Both mortality and syncope recurrence increased significantly with age ($P = 0.006$ and $P = 0.008$, respectively) (Table 1). Figure 1 shows the Kaplan–Meyer curves of mortality and syncope recurrence stratified for type of syncope. Mortality was highest in patients affected by cardiac-type syncope, and syncope recurrence was more frequent in patients with neuro-mediated syncope albeit not significantly so ($P = 0.252$ and $P = 0.678$, respectively). At Cox regression analysis, mortality was significantly related to age (hazard risk: 1.17, 95% confidence interval: 1.01–1.37, $P < 0.05$) and comorbidity (hazard risk: 1.39, 95% confidence interval: 1.01–1.93, $P = 0.044$), whereas syncope recurrence was associated with age (hazard risk: 1.13, 95% confidence interval: 1.01–1.25, $P = 0.023$) and BADL disability (hazard risk: 1.30, 95% confidence interval: 1.04–1.25, $P < 0.035$).

Clinical changes in elderly patients with syncope at the end of follow-up

At the 2-year evaluation, BADL lost had significantly increased from a baseline of 0.55 ± 0.97 to 1.04 ± 1.57 ($P = 0.0003$). Also IADL lost tended to increase, but not

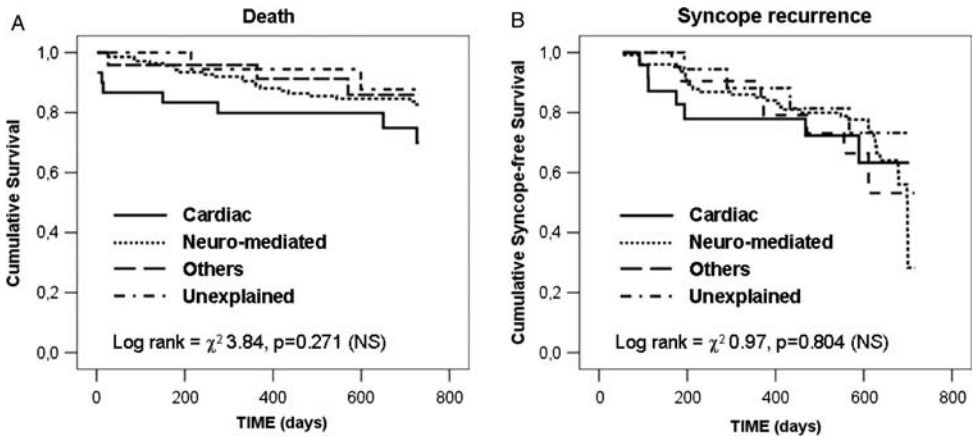

Figure 1. Kaplan–Meyer curves of mortality (A) and syncope recurrence (B) stratified for type of syncope (other: drug-induced and multifactorial).

significantly (1.76 ± 2.96 versus 2.36 ± 3.23; $P = 0.08$). Moreover, disability in IADL but not in BADL, significantly increased during follow-up in patients with recurrent syncope (1.93 ± 3.14 versus 3.47 ± 3.2; $P = 0.008$). The MMSE score remained stable throughout the study (26.1 ± 9.5 versus 26.9 ± 3.8; $P = 0.321$). In contrast, the GDS score significantly increased from a baseline of 3.73 ± 3.67 to 5.59 ± 5.76 at last evaluation ($P < 0.0001$). Accordingly, the mean percentage incidence of depressed patients (GDS score ≥ 6) increased from 28.3% at baseline to 41.4% ($P < 0.001$). However, the CIRS score in patients with depression did not differ between baseline and the last evaluation (8.0 ± 2.8 versus 7.7 ± 2.8, $P = 0.344$). Similarly, syncope recurrences did not differ between patients with ($n = 47$) and those without ($n = 67$) depression ($P = 0.445$). At the end of follow-up, the mean percentage of hospitalisations was 38.3% (36.4 versus 39.3% in patients with or without syncope recurrence; $P = 0.321$) and the mean percentage of falls was 25.2% (24.2 versus 25.7% in patients with or without syncope recurrence; $P = 0.245$).

Discussion

In this study of elderly patients with syncope, the 2-year total mortality was 18%. Syncope recurrence occurred in 33% of elderly patients. Cardiac syncope was more frequent in deceased patients than in survivors. Neuro-mediated and unexplained syncope did not differ between the two groups, whereas drug-induced and/or multifactorial syncopes were less frequent in patients with syncope recurrence. Mortality and syncope recurrence increased significantly with age. Multivariate analysis showed that age and comorbidity predict mortality, whereas age and disability predict syncope recurrence. Finally, depressive symptoms increased from the baseline to the end of follow-up.

Mortality in elderly patients with syncope

The overall 2-year mortality in our patients was 18%, whereas it was 35% in the oldest subgroup of patients (i.e. those between 80 and 89 years). Our deceased elderly patients with syncope had several characteristics typical of 'frail' elderly patients (16). In fact, they were older, took more drugs, had the lowest BMI and MMSE score and, more importantly, they had the highest comorbidity. Elderly patients had the greatest CIRS value and the multivariate analysis confirmed the pivotal role of comorbidity in syncope-induced mortality.

Unfortunately, we are unable to determine whether our elderly patients with syncope differ from the elderly of the general population.

Mortality and syncope types in the elderly

Several groups have investigated the relationship between mortality and syncope aetiology. Kapoor *et al.* showed that overall mortality and the incidence of sudden death from cardiovascular causes were similar in the elderly and in the young, whereas overall mortality and the incidence of sudden death from non-cardiovascular and/or unknown case of syncope were higher in the elderly [9]. Dougnac *et al.* demonstrated that cardiovascular syncope mortality was higher than that of other kinds of syncope (28.3 versus 8.9%) [15]. Getchell *et al.* reported that mortality from cardiac syncope and from iatrogenic syncope was higher in the elderly (66 and 50%) than in young people (28 and 26%); the same applies to reflex syncope (14% in individuals aged ≥ 70 years and 4% in <70 years) [7]. Roussanov *et al.* found that cardiac syncope in elderly patients entailed the highest risk for all-cause mortality and for cardiovascular mortality [8]. Finally, the low mortality in the USA NIS study suggests that vasovagal syncope may have occurred in a large proportion in this cohort [5].

In our study, only cardiac syncope discriminated between deceased and survivor patients, whereas neuro-mediated and unexplained syncope were similar in the two groups. However, at multivariate analysis, the type of syncope was not predictive of mortality. Since most syncopes were neuro-mediated (65%) and did not influence mortality or recurrence at univariate analysis, these findings may explain the lack of significance at multivariate analysis.

Syncope recurrence in the elderly

Getchell *et al.* observed a high prevalence of syncope recurrence especially in patients affected by neuro-mediated and unknown syncope during the first year of follow-up [7]. Roussanov *et al.* reported that the correlation between syncope recurrence and age was stronger than the correlation between syncope recurrence and aetiology; syncope recurrence occurred in the middle-aged group (30–60 years, 29%) and in the very elderly (older than 75 years, 31%) [8]. In our study syncope recurred in 32.5% of all patients and was unrelated to syncope aetiology, with the exception of drug-induced and multifactorial syncopes, which were related to fewer recurrences probably consequent to appropriate treatment after the diagnosis. In addition, our elderly patients with syncope recurrences were older, and the most cognitively impaired and disabled individuals. Patients affected by cognitive impairment may not comply with medication or their physician's indications. Disabled patients also find it more difficult to sit or lie down in case of syncope. In fact, age and disability were predictive of syncope recurrence at multivariate analysis. In a previous study, patients who developed syncope were initially more functionally disabled and they subsequently lost function more frequently than those without syncope [6].

Hospitalisations, falls, fractures and depression in elderly patients with syncope

Hospitalisations decreased while mortality and syncope recurrence increased with age. Accordingly, deceased

patients and syncope recurrence were lower in hospitalised patients. This paradoxical phenomenon may reflect the reluctance to hospitalise patients with very advanced age [16]. It is also noteworthy that the prevalence of falls and fractures were similar in our patients with and without syncope recurrence. It is difficult to explain this observation. Cardiovascular syncope is one of the most common causes of falls in the elderly [17]. Our results could be attributed either to a low incidence of cardiac syncopes (15%) or to better prevention of falls and/or fractures after the first episode of syncope. We found that depressive symptoms increased during follow-up. The relationship between depressive status and comorbidity in the elderly is well known [18]. Depression is a characteristic of neuro-cardiogenic syncope which, in turn is characterised by a high incidence of syncope recurrences [19]. However, depressive symptoms were not correlated with comorbidity or syncope recurrences in our sample.

Limitations of the study

A small sample size is the main limitation of our study. In fact, a very large group would be needed to demonstrate differences in such findings as fracture rate in elderly patients with syncope. Second, we did not compare our results with data of the normal non-syncopal elderly population. Consequently, the significance of several results is uncertain. Third, the number of patients with cardiac syncope is small (n = 30), and therefore, the increase in cardiac syncope in deceased patients is of borderline statistical significance using Student's t-test performed without adjustments for potential confounders. When multivariate analysis adjusted for age, sex and comorbidity was performed, cardiac syncope predicted mortality by 2.77 (95% CI: 0.23–32.4), whereas non-cardiac syncope (neuro-mediated and others) by 1.94 (95% CI: 0.22–17.1). The small number of patients with cardiac syncope may explain why we did not find any significant difference in mortality between cardiac and non-cardiac syncope. This lack of difference could also be due to underdiagnosis of cardiac syncope. In fact, the cause of death was known only in a few patients (i.e. 23.5% in cardiac syncopes).

Conclusions

In our study, overall syncope mortality and recurrence was 18 and 33%, respectively. Mortality was highest in the oldest patients and in those with cardiac syncope while syncope recurrence was low in drug-induced and/or multifactorial syncope. Age was found to be a predictor of both mortality and syncope recurrence. Moreover, mortality and syncope recurrence were predicted by comorbidity and disability, respectively. Importantly, the incidence of depressive symptoms increased in elderly patients with syncope. Finally, early identification of drug-induced and/or multifactorial syncope can prevent syncope recurrence.

Key points

- After a 2-year follow-up, the mortality in elderly patients with syncope was 18% and syncope recurrence was 33%.
- Cardiac syncope was more frequent in deceased patients than in survivors.
- Syncope recurrence was high despite a low incidence of unexplained syncope.
- Comorbidity and disability are predictive of syncope and syncope recurrence, respectively.

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Conflicts of interest

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Testing homocysteine-induced neurotransmitter deficiency, and depression of mood hypothesis in clinical practice

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Abstract

Background: high total plasma homocysteine (tHcy) levels may cause neurotransmitter deficiency, and consequently depression of mood. We have recently shown that mixed oral nutritional supplements containing B-group vitamins led to a statistically significant benefit on depressive symptoms. The aim of this report was to examine the association between elevated plasma tHcy and symptoms of depression in older patients.
Methods: two-hundred and thirty-six hospitalised acutely ill older patients, who were part of a randomised double-blind placebo-controlled trial, were assigned to receive daily mixed oral nutritional supplements containing B-group vitamins or a placebo for 6 weeks. Outcome measures included symptoms of depression measured using Geriatric Depression score and plasma tHcy levels.
Results: the mean tHcy concentration fell by 22% among patients given the supplements compared with the placebo group (mean difference 4.1 μmol/l (95% CI: 0.14–8.03), $P = 0.043$). tHcy concentrations was divided into four quartiles and analysed against depression scores. tHcy concentrations in the first relative to the fourth quartile of the distribution were associated with a lower depression symptoms at the end of the supplement period (Geriatric depression score $r = –0.20$, $P = 0.042$).
Conclusions: lower plasma tHcy concentrations were associated with reduced depression symptoms in older patients recovering from acute illness.

Keywords: *depression, homocysteine, B vitamins, older people nutrition, nutrition supplements*