Risk factors for one-year all-cause mortality in elderly multimorbid medical in-patients.

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Abstract

Background: Due to expansion of longevity, the proportion of elderly people with multimorbidity is increasing. Our aim was to identify risk factors for all-cause mortality in elderly multimorbid medical in-patients one year after acute hospitalization. Information regarding risk factors is important to support targeted care plans after discharge.

Methods: Prospective cohort study of patients acutely admitted to a medical department in a Norwegian regional hospital. Eligible patients were community-dwelling, received home care services before hospitalization, were aged 75+, and suffered from two or more chronic conditions. Inclusion period was 1. April – 31. October 2012. Candidate variables were number of daily prescribed drugs, Cumulative Illness Rating Scale for Geriatrics score, delirium, body mass index (BMI), handgrip strength, Barthel Activities of Daily Living Index score, and the laboratory analyses haemoglobin (Hgb), sodium (Na) and estimated glomerular filtration rate (eGFR).

Results: We included 227 patients; mean age 86 years, 59% women, 71% lived alone. During the year after hospitalization, 39% died. In the adjusted cox proportional hazards regression analysis, significant and independent risk factors were BMI (hazard ratio (HR) 0.93, 95% confidence interval (CI) 0.88-0.98 per kg/m²), Hgb (HR 0.87, 95% CI 0.76-0.98 per g/100 mL), Na (HR 0.94, 95% CI 0.90-0.99 per mmol/L) and eGFR < 60 mL/min/1.73 m² (HR 1.82, 95% CI 1.07-3.08).

Conclusions: In this cohort of multimorbid elderly internal medicine patients, low body mass, hyponatremia, impaired renal function and anaemia were identified as independent and significant risk factors for one-year mortality.

Background

Due to expansion of longevity, the population is aging worldwide. With increasing life expectancy, the proportion of people with multimorbidity will increase (1-3). Multimorbidity increases the risk of death and influences the individual life expectancy (4). Other important factors influencing risk of death among community dwelling elderly patients are, among others, polypharmacy (5), frailty (6), functional (7) and cognitive decline (8). Hospital admissions may accelerate functional decline (9, 10) and is associated with increased mortality (11). Weight loss, chronic conditions like heart failure, chronic obstructive pulmonary disease and impaired renal function are important additional factors that influence life expectancy in elderly patients (12-17). However, little is known regarding how these prognostic factors act in combination regarding risk for mortality in elderly people with multimorbidity.

Frailty and sarcopenia are symptom complexes closely related to hospital admission, longer hospital stay, physical disability, poor quality of life (18), and increased 30-days and one-year mortality (19). Handgrip strength (HGS) is an indicator of sarcopenia, and low HGS has been shown to be a good clinical marker of poor mobility and displays a linear relationship with the risk of incident disability (20).

Moreover, longer hospital stay is related to a more pronounced loss of function and higher mortality (21, 22).

The impact of cognitive impairment on survival after hospitalization is less consistent. A previous study indicated that patients with dementia have the same 3-months mortality after acute hospitalization for trauma as cognitively intact patients (23). However, in heart failure patients, it has been reported higher mortality and readmission rates 6 months post discharge when the combination of low HGS and cognitive impairment was present (24). Moreover, delirium occurring during hospitalization is a known risk factor for post-discharge adverse events and mortality (25).

Laboratory measurements are easy accessible and can give useful information. Anaemia is frequent and shows increasing prevalence in elderly people (26). Anaemia is known to affect cognition and emotions, and leads to impaired function (27). Electrolyte disturbances are also frequent among elderly patients, and hyponatremia is most common (28). Changes in electrolyte concentration affects alertness, reduces cognition (29) and increases mortality (30, 31). For patients with chronic kidney disease, hyponatremia will worsen the prognosis (32).

It is important to identify risk factors for all-cause mortality in frail old hospitalized patients in order to support targeted care planning after discharge. Therefore, the aim of the present study was to identify risk factors for all-cause mortality in elderly multimorbid medical in-patients one year after acute hospitalization.

Methods

Six of twelve municipalities in the Norwegian county Vestfold (221,100 inhabitants in the county whereof 151,300 in the six target municipalities) were invited to participate in this study of elderly patients who were acutely admitted to the medical department of Vestfold Hospital Trust.

Selection criteria

During April–October 2012, a project nurse used lists of emergency admissions to consecutively recruit patients who met the following inclusion criteria: home-dwelling, aged 75 years or more, received home care services, suffered from at least two chronic conditions, and lived in one of the six target municipalities. Patients not able to give informed consent, who were terminally ill, or who lived in a long term care facility prior to admission, were excluded.

Data collection

Possibly eligible patients were approached by the project nurse as soon as possible after admission, normally the day after. Independence in personal activities of daily living (ADL) was assessed by the Norwegian version of the Barthel Index (33). The Mini-Mental State Evaluation - Norwegian Revised Version (MMSE-NR) (34) was used as a cognitive screening. The Informant Questionnaire of Cognitive Decline in the Elderly (IQCODE) was obtained by calling the closest relative of the patient. Height and

weight were measured and Body Mass Index (BMI) was calculated. HGS was assessed in both hands using a Jamar dynamometer. Patients who were able to get out of bed performed the test sitting on a chair. Bedridden patients were assessed in a sitting position with the backrest elevated. The patient was instructed to squeeze the handle as forcefully as possible for 5 seconds. The mean value of three trials was used, both right and left hand were measured, and the mean value of the strongest hand (measurement in kg) was utilised in the statistical analyses.

Two physicians, one consultant specialized in geriatric medicine and old age psychiatry and one resident in geriatric medicine, scrutinized all medical records of the included patients. Complete information regarding the current acute hospital admission, prior admissions and medications at the time of admittance was retrieved from the referral letter, the electronic patient records and the patient administrative system. The Cumulative Illness Rating Scale for Geriatrics (CIRS-G) was scored for each patient. As part of the review of the case notes, symptoms of delirium and cognitive decline was particularly noted as these symptoms often pass unnoticed in hospitals.

The patients' present drug use at the time of admittance was obtained from the medical records, the referral letter and the ward notes. A pharmacist registered all drugs according to the Anatomical Therapeutic Chemical classification system (ATC-code). A study nurse visited the patients three weeks post discharge and measured height, weight and HGS, and a new MMSE-NR test was carried out. Time of death was recorded using the Norwegian death registry.

Laboratory measurements

Blood samples were drawn as part of the clinical routine. Laboratory measurements selected for statistical analysis were haemoglobin (Hgb), sodium (Na) and estimated glomerular filtration rate (eGFR). Hgb was measured on either Sysmex XE2100 or Sysmex XE 5000 (Sysmex Europe) with reagents from the supplier. Serum Na and serum creatinine were analysed on Vitros 5.1 (Ortho-Clinical Diagnostics, USA) with reagents from the supplier. GFR was estimated using the Modification of Diet in Renal Disease equation (35).

Statistical analyses

Distribution plots were examined for all variables to look for outliers and deviance from normal distribution. The central tendency and variation of normally distributed variables are described by the mean and the standard deviation (SD), and by the median and the interquartile range (IQR) for non-normally distributed variables. Kolmogorov-Smirnov's test of normality was used.

For comparison between groups, the independent sample t-test was performed for normally distributed variables and the Mann-Witney U test for non-normally distributed variables.

For unadjusted and adjusted analyses of one-year mortality we used the Cox proportional Hazards method. We included variables related to function (Barthel Index, HGS, and MMSE-NR), comorbidity (CIRS-G and number of drugs), nutritional status (BMI) and the laboratory measurements Hgb, Na and

eGFR. All variables with a p-value ≤ 0.10 in unadjusted analyses were included in the multivariate analysis. Number of drugs, BMI, MMSE-NR score, HGS, Hgb and Na were treated as continuous variables in univariate and multivariate analyses, whereas the Barthel Index score was highly skewed and was thus dichotomized (0-12 and 13-20). The hospital laboratory displayed the results for eGFR as a value between 1 and 60 or ≥ 60 , hence, GFR was dichotomized with 60 as the threshold value. Due to gender dependent results for HGS, this variable was analysed separately for men and women.

For Kaplan-Meier plots, explanatory variables were categorized. For BMI we made three groups with cut offs as published by Gulsvik et al. (< 22.0 , $22.0 - 27.9$ and ≥ 28.0 kg/m²) (12). Hgb was dichotomized as below and above 12 g/100 mL according to Culleton et al. (36). Na was dichotomized as below and above 137 mmol/L, and eGFR as below and above 60 mL/min/1.73 m².

All tests were two-tailed and carried out using SPSS version 23. The level of significance was set to 5%.

Results

We included 227 patients. For details of inclusion and exclusion see Figure 1. The mean age of the participants was 86 years, 134 (59%) were women, and 162 (71%) lived alone (table 1). One year after hospitalization, 89 (39%) were deceased. Survivors and non-survivors at one-year are compared in Table 1. There was no statistically significant difference between the two groups regarding age and gender. At admittance the survivors had higher BMI, better cognitive function, less comorbidity and managed more daily living activities than non-survivors. They also had higher Na and eGFR values, and fewer developed delirium during the hospital stay. For HGS and number of drugs used, we found no difference.

In bivariate Cox regression analyses, variables significantly associated with one-year mortality were lower body mass, anaemia, hyponatremia, impaired renal function, reduced cognitive function, delirium during admission, more comorbid conditions and dependency in daily living (table 2).

Due to missing in some of the variables, 213 patients were included in multivariate analyses. The comorbidity of the 14 patients not included was below average in the population with a mean CIRS-G score of 19.8 (SD 5.4), they were at the same age mean 86 years (SD 5.0) and used the same amount of drugs regularly (mean SD) 8 (3) drugs). In adjusted Cox proportional Hazards regression analyses, we found lower BMI, lower Na, lower eGFR and lower Hgb to be significantly and independently associated with one-year mortality (Table 2).

Figure 2 (a-d) displays the Kaplan-Meier survival curves for the significant predictors of one-year mortality; BMI, Hgb, Na and eGFR.

Discussion

In our population of elderly medical in-patients, we found low values for BMI, Na, eGFR and Hgb to be independent and statistically significant risk factors for one-year mortality.

In contrast to the commonly reported J or U shaped associations between BMI and survival with higher mortality at both extremes (16, 17), we found a close to linear relationship. The patients with the highest BMI had the best survival chance. One previous Norwegian cohort study reported the same pattern, with the highest mortality in patients with BMI < 20 kg/m² (12). A meta-analysis of BMI and mortality in persons aged > 65 from 2017 demonstrated increased mortality in persons with a BMI < 22 kg/m² and the lowest mortality risk in persons with BMI 28-29 kg/m². On the other extreme, an increased mortality risk was first reached when BMI exceeded 33 kg/m² (37). Among our patients, only 7 had a BMI of that magnitude, reducing our possibility to find an excess mortality risk associated with high BMI. In particular for multimorbid patients, our findings support that a high BMI seems to be beneficial. For treatment plans after discharge we suggest to emphasize information regarding weight and nutritional status.

Anaemia is frequent in individuals living in the community and the prevalence is increasing in elderly people (26). Anaemia in the elderly affects cognition, emotions and leads to impaired function (38). In our patient population, anaemia was significantly associated with one-year mortality. A German initiative has proposed to include anaemia as a geriatric syndrome (38). Our results supports this, and we recommend that assessment of anaemia becomes a natural part of the patient's treatment plan after discharge.

Hyponatremia is the most common electrolyte abnormality observed in clinical practice (28). Hyponatremia is related to several chronic diseases whereof some have an increasing prevalence with increasing age, like stroke, heart disease, chronic kidney disease and cancer. Normal symptoms for patients with hyponatremia include dizziness, disturbed alertness and confusion, which increases the risk of falls (29). Patients with hyponatremia have longer stays, more readmissions and increased mortality (30-32, 39). One of the major causes of hyponatremia is diuretic therapy, often in combination with psychoactive drugs. Many elderly use at least one diuretic drug (40). Our suggestion is that patients with polypharmacy and hyponatremia should get a thorough medication review.

eGFR is one of the most used ways to measure kidney function, and has been shown to be related to mortality in different patient groups (13) and at different stages of disease (14, 15). In older patients, a low eGFR might be regarded as much as a marker for age-related loss of physiologic reserves than as a predictor of specific renal outcomes. It appears, however, also to exist a reciprocal relationship between aging and chronic kidney disease, as the presence of geriatric complications is also high in younger patients with end stage renal disease (41). For elderly multimorbid patients, it is important that eGFR is measured and the result is taken into account when deciding on treatment goals and drug therapy.

Most of our risk factors candidates are considered as frailty indicators (42). Frailty has been shown to be associated with higher mortality, longer in-hospital stay and more complications, also in individuals without multimorbidity (19, 21, 43). Moreover, previous studies have found multimorbidity (3), polypharmacy (5, 44), functional decline (7), low handgrip strength (20), sarcopenia (18, 45) and cognitive decline (8) to be associated with one-year mortality. None of these frailty indicators were associated with one-year mortality in our study population. In contrast to other studies that have included more unselected patients (45-47), our aim was to study mortality in selected patients that all suffered

from mild to severe frailty. Our inclusion criteria (multimorbidity and dependence upon home nursing) were chosen accordingly. More than 40 % scored underneath the threshold for being “weak” according to the European Working Group on Sarcopenia in Older People definition (48), and many were cognitively impaired as indicated by a median MMSE-NR score of 23. Cognitive impairment and multimorbidity interact negatively and have impact on older adults’ health status, quality of life and survival (49). Our findings should be interpreted bearing in mind that the studied cohort represents a selection of a mildly to more severely frail subsample of elderly hospitalised patients.

Our results support the consistent previous findings regarding an increased risk of mortality among individuals with low BMI, hyponatremia, impaired renal function and low Hgb. It is likely that these factors are indicators for disease or frailty that contribute to mortality. Hence, we suggest these four elements always to be assessed and considered as part of every treatment plan for frail elderly discharged from hospital, and for patients on polypharmacy these abnormalities should give extra attention during the medication review.

Strengths and limitations

This research project was a cooperation between six municipalities and the hospital. In order to be included, the patients had to receive home care services prior to the admission. These inclusion criteria might have increased the proportion of patients with a limited social network, a group that have a higher risk of complications and mortality. For ethical reasons, the patients had to be competent to give a valid, signed consent, obviously limiting the generalizability to patients with severe dementia and psychiatric disorders. Compared to previous studies, our population is older and has more pronounced multimorbidity and polypharmacy. We had a limited follow up, thus we were not able to register possible drug-related deaths or deaths related to acute illness during the year after inclusion. We also have no information on drug changes or visits to the primary health care physician.

Our population was old, with a mean age of 86 years, and thus representative for a geriatric patient group. The hospital is governmental financed, offering health services to all inhabitants regardless of economic or social status, thus giving a less selected sample than would else have been possible. The patients were frail and weak (48), representing a population that frequently is excluded from research. Compared to other studies, our study comprised patients with more severe comorbidity, lower muscle strength, a more pronounced polypharmacy and, accordingly, a high one year mortality. This weakens the generalizability of the results to all elderly, but it reinforces the validity for frail elderly patients.

Conclusion

In multimorbid elderly internal medicine patients, underweight, hyponatremia, impaired renal function and anaemia were identified as independent and significant risk factors for one-year mortality. It is likely that these factors are indicators for disease or frailty that contribute to mortality. We suggest these four elements always to be assessed and considered as part of every treatment plan for frail elderly persons discharged from hospital.

List Of Abbreviations

ADL Activities of daily living

ATC The Anatomical Therapeutic Chemical classification system

BMI Body Mass Index

CIRS-G The Cumulative Illness Rating Scale for Geriatrics

eGFR estimated Glomerular Filtration Rate

Hgb Haemoglobin

HGS Handgrip Strength

IQCODE The Informant Questionnaire of Cognitive Decline in the Elderly

IQR Interquartile Range

MMSE-NR Mini Mental State Evaluation-Norwegian Revised Version

Na Sodium

SD Standard Deviation

Declarations

Ethics approval and consent to participate.

Written informed consent was obtained from all the participants in accordance with Norwegian legal regulation. The study was presented for the Regional Committee for Medical Research Ethics and approved by the Norwegian Social Science Data Services.

Consent for publication

Not applicable

Availability of data and materials

The datasets used for the current study are available from the corresponding author upon reasonable request

Competing interests

The authors declare no conflict of interest.

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Author contributions

MWH and TBW conceived and designed the study, MWH, HK and TBW interpreted the data, and MWH drafted the manuscript, which was critically revised by all authors. All authors had access to the complete study data and had a say in the manuscript preparation, approval of the final version and the decision to submit for publication.

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Tables

Table 1: Characteristics of the participants, N=227

	Patients dead within one year n=89	Patients alive after one year n=138	Difference between the study groups p*
Age, years. Median (IQR)	86 (80 - 90)	86 (81 - 91)	0.731
Female gender. N (%)	53 (60)	81 (59)	0.898
Living alone. N (%)	62 (70)	100 (73)	0.649
Barthel ADL Index. Median (IQR) n=223	11.9 (7 - 16)	13.8 (10 - 17)	0.006
BMI, kg/m ² . Median (IQR) n=217	22.4 (19.7 - 25.5)	24.3 (20.9 - 29.6)	0.002
MMSE-NR. Median (IQR) n=223	22.0 (18 - 26)	23.7 (20 - 28)	0.014
HGS, kg. Mean (SD). Women n=106	10.8 (4.8) ^a	11.1 (5.0) ^a	0.772
HGS, kg. Mean (SD). Men n=75	19.9 (7.2) ^b	22.7 (9.6) ^b	0.167
Number of daily medications. Median (IQR)	8.5 (6 - 11)	7.6 (5 - 9)	0.074
CIRS-G total score. Median (IQR)	23 (19 - 27)	21 (16 - 25)	0.003
Delirium during index stay. N (%)	38 (43)	33 (24)	0.003
Haemoglobin, g/100 mL. Mean (SD)	10.4 (1.9)	11.4 (1.8)	<0.001
Sodium mmol/L. Median (IQR)	135 (133 - 139)	137 (135 - 140)	0.005
eGFR, mL/min/1.73m ² . Median (IQR) n=226	45 (30 - 60)	49 (39 - 60)	0.024

ADL = Activities of Daily Living, BMI = Body Mass Index, MMSE-NR = Mini Mental State Examination - Norwegian Revised Version, HGS = Hand Grip Strength, CIRS-G = Cumulative Illness Rating scale for Geriatrics, eGFR = Estimated Glomerular Filtration Rate.

*Chi-square for categorical variables. Independent sample t-test for continuous variables.

^aFemales: 47 patients dead and 59 alive.

^bMales: 31 patients dead and 44 alive.

Significant differences, $p < 0.05$, in bold font

Table 2: Unadjusted and adjusted Cox proportional hazards regression models for predictors of one-year mortality (n=213)

	Unadjusted risk for death			Adjusted risk for death		
	HR	95%CI	p	HR	95%CI	p
Age, years.	0.99	0.96 - 1.03	0.727	---	---	---
Female gender	1.05	0.69 - 1.61	0.812	---	---	---
Living alone	1.12	0.71 - 1.75	0.637	---	---	---
Barthel ADL Index ≤ 12	1.71	1.12 - 2.62	0.013	1.23	0.77 - 1.95	0.392
BMI, kg/m ²	0.92	0.88 - 0.97	0.002	0.93	0.88 - 0.98	0.006
MMSE-NR	0.96	0.92 - 1.00	0.026	0.97	0.92 - 1.02	0.197
HGS, kg. Women	0.99	0.94 - 1.06	0.982	---	---	---
HGS, kg. Men	0.97	0.93 - 1.01	0.170	---	---	---
Number of prescribed drugs	1.05	0.99 - 1.11	0.109	---	---	---
CIRS-G total score	1.05	1.01 - 1.09	0.008	1.03	0.98 - 1.07	0.243
Delirium during index stay	1.80	1.18 - 2.74	0.006	1.19	0.70 - 2.01	0.523
Haemoglobin, g/100mL	0.79	0.71 - 0.87	<0.001	0.87	0.76 - 0.98	0.027
Sodium, mmol/L	0.95	0.92 - 0.98	0.004	0.94	0.90 - 0.99	0.026
eGFR < 60 mL/min/1,73m ²	1.59	1.02 - 2.48	0.041	1.82	1.07 - 3.08	0.026

ADL = Activities of Daily Living Index, BMI = Body Mass Index, MMSE-NR = The Mini Mental State Examination - Norwegian Revised Version, HGS = Hand Grip Strength, CIRS-G = Cumulative Illness Rating Scale for geriatrics, eGFR = Estimated Glomerular Filtration Rate.

Significant differences, $p < 0.05$, in bold font

Figures

Figure 1

Patient flow.

Figure 2

Kaplan Meier plots for one-year survival by a) BMI, b) Haemoglobin, c) eGFR and d) Sodium. a) BMI, n = 217, no cases were censored. b) Haemoglobin, n = 227, no cases were censored. c) eGFR, n = 226, no cases were censored. d) Sodium, n = 227, no cases were censored.