PREDICTION OF CARDIOVASCULAR MORTALITY IN FUNCTIONALLY DISABLED ELDERLY – A POSSIBLE NEW SCORE

KARDIOVASKULARNI MORTALITET KOD FUNKCIONALNO ZAVISNIH STARIH OSOBA – MOGUĆI PREDIKTIVNI SKOR

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Summary

Background: We investigated the traditional and new biomarkers as predictors of cardiovascular mortality in the functionally disabled elderly who are living in a community.
Methods: This prospective study included 253 participants (78.3% women) aged 65 and over who were monitored for 32 months. Receiver operating curve analysis and the Cox proportional hazard model were used to identify univariate and multivariate predictors of cardiovascular mortality. The Kaplan-Meier survival curve and Log rank test were used for survival analysis.
Results: During the study, 43.1% participants died from cardiovascular diseases. Cutoff points of multivariate predictors were used to build a score system. The risk score was positive in patients with three or more of the following predictors: albumin <40 g/L, body mass index <25 kg/m^2, total serum bilirubin <10.5 μmol/L, blood urea nitrogen ≥6.5 mmol/L and high-sensitivity C-reactive protein ≥2.25 mg/L. The relative risk for cardiovascular mortality for someone with a positive vs. negative score was 3.91 (95% CI: 2.55–5.98;

Kratak sadržaj

Uvod: Istraživali smo tradicionalne faktore rizika i nove biomarkere kao prediktore za kardiovaskularni mortalitet kod funkcionalno zavisnih starih osoba koje žive u zajednici.
Metode: Ova prospektivna studija obuhvatila je 253 učesnika starih 65 i više godina (78,3% žena) koji su praćeni 32 meseca. ROC kriva (engl. receiver operating characteristic curve) i Coxov proporcioni hazardni model korišćeni su za identifikaciju univarijantnih i multivarijantnih prediktora kardiovaskularnog mortaliteta. Kaplan-Meierova kriva preživljavanja i Log rank test korišćeni su za analizu preživljavanja.
Rezultati: Tokom studije 43,1% učesnika je umrlo od kardiovaskularnih bolesti. Na osnovu graničnih (*cutoff*) skorova multivarijantnih prediktora napravljen je prediktivni skor za kardiovaskularni mortalitet. Ovaj skor je bio pozitivan kod učesnika sa tri i više od sledećih prediktora: albumin <40 g/L, indeks telesne mase <25 kg/m^2, ukupni serumski bilirubin <10,5 μmol/L, urea ≥6,5 mmol/L i visokosenzitivni C-reaktivni protein ≥2,25 mg/L. Relativni rizik za kardiovaskularni mortalitet ukoliko neko ima pozitivan skor bio

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Abbreviations: ADL, Activities of daily living; BMI, body mass index; BUN, blood urea nitrogen; CCI, Charlson Comorbidity Index; HbA1c, hemoglobin A$_{1c}$; HDL-c, high density lipoprotein cholesterol; HsCRP, high sensitivity C-reactive protein; IADL, instrumental activities of daily living; IMRIS, Inflammatory-Malnutrition-Renal Involved Score; LDL-c, low density lipoprotein cholesterol; MACE, major cardiovascular event; ROC, receiver operating characteristic curve; RR, relative risk.

P<0.001). There was no change in risk after adjustment for age, sex, traditional cardiovascular risk factors, comorbidities and a number of disabilities.

Conclusions: Presence of low grade inflammation, malnutrition and early signs of renal dysfunction are essential for cardiovascular risk among the functionally disabled elderly and may be assessed using the proposed new inflammatory-malnutrition-renal involved score (IMRIS).

Keywords: cardiovascular risk, C-reactive protein, elderly, malnutrition

je 3,91 (95% CI: 2,55–5,98; P<0,001). Nije bilo promene u riziku nakon prilagođavanja za starost, pol, tradicionalne faktore rizika, komorbiditete i stepen funkcionalne zavisnosti.

Zaključak: Prisustvo inflamacije niskog stepena, malnutricije i početni znaci bubrežne disfunkcije su esencijalni za procenu kardiovaskularnog rizika kod funkcionalno zavisnih starih osoba i mogu biti procenjeni na osnovu novog prediktivnog skora nazvanog IMRIS (engl. inflammatory-malnutrition-renal involved skor).

Ključne reči: C-reaktivni protein, kardiovaskularni rizik, malnutricija, stare osobe

Introduction

Cardiovascular mortality is the leading cause of death in elderly people (1). It is already known that the traditional cardiovascular risk factors are not the principal predictors for cardiovascular events in the elderly (2–4). Studies have shown that some of these risk factors even act in the reverse direction with the oldest people (≥85 years) (5). This is the case with total cholesterol (6), and the body mass index (7, 8). There was no positive association between overweight and all-cause and cardiovascular mortality in individuals aged 65 years and older. On the contrary, a low body mass index (BMI) was consistently associated with increased risk for mortality in the elderly (9). Weight loss in older adults is highly predictive of increased morbidity and mortality (10, 11).

A decrease in body protein is a major characteristic of ageing (12). Protein-energy wasting (PEW) is diagnosed if three characteristics are present (low serum levels of albumin, transthyretin, or cholesterol), reduced body mass, and reduced muscle mass. It involves mainly muscle proteins, and is associated with decreased muscle strength and functional impairment (12). The functionally disabled elderly are a large proportion of the growing population of elderly. According to epidemiologic studies, 20% of older persons over 65 years require assistance with the Activities of Daily Living (ADLs); 45% of older persons over 85 years require assistance with the ADLs (13). They are vulnerable groups of elderly who are at high risk of cardiovascular mortality.

Hypoalbuminemia is the most commonly used surrogate of PEW (14). Low albumin may be associated with hypercoagulable states (12), and increased blood viscosity (12). Serum albumin is a major determinant of plasma oncotic pressure and the presence of hypoalbuminemia may reduce the threshold for development of pulmonary edema in patients with heart failure (HF) (15).

Hypoalbuminemia is an independent predictor of incident HF among community-dwelling older adults and may provide important information for elderly patients with acute decompensated HF (16).

Acute heart failure syndrome (AHFS) in elderly patients eventually ends with death from a cardiovascular cause. In AHFS, renal dysfunction carries a poor prognosis. Altered renal hemodynamic due to hemodynamic, neurohormonal, and inflammatory factors in addition to further activation of neurohormones (renin-angiotensin-aldosterone system, catecholamines, endothelin, vasopressin) and prostaglandin inhibition contribute to arteriolar glomerular vasoconstriction and urea without creatinine reabsorption in the distal nephron. This may be the explanation why elevated blood urea nitrogen is such a strong risk factor for cardiovascular mortality in elderly (17).

It has become apparent that many abnormalities in the protein-energy nutritional status can also be induced by inflammatory processes (14). Moreover, loss of muscle and fat stores and inflammation are likely to increase the risk of death from cardiovascular or cerebrovascular disease (possibly by promoting vascular endothelial damage) (14). Low dietary intake and diminished muscle mass are both common in the old individuals and may cause low values of blood urea nitrogen (BUN) and serum creatinine, even in the presence of advanced renal failure (12). On the other hand, an elevated BUN concentration seems to be an important predictor of poor outcome in patients with HF (18).

Ageing is associated with the activation of the entire inflammatory cascade. Inflammatory markers such as C-reactive protein, interleukin 6 and fibrinogen are all positively correlated with cardiovascular death. Inflammation and malnutrition are related (19), and in many studies they were included together in cardiovascular risk scores (malnutrition-inflammation-atherosclerosis (MIA) syndrome, prognostic inflammatory and nutritional index (PINI), etc.) (20, 21). These risk scores are applicable in vulnerable patients, like patients on dialysis or patients with end-stage chronic diseases (22).

It is possible that the biomarkers of inflammation are more strongly related to vascular risk in aged people than the measures of plasma lipids, or other established risk factors (23, 24). There is an inverse relationship between bilirubin (total and direct) and high-sensitivity C-reactive protein (hsCRP) among apparently healthy Korean adults (25). Hwang et al. (25) suggested that a low serum CRP level may be

due to the antioxidant and antiinflammatory effects of bilirubin metabolism (25). Low total serum bilirubin is associated with coronary artery calcification (CAC), and with the presence of angiographically documented coronary heart disease (CHD) after adjustment for the established risk factors (26). Men without atherosclerotic cardiovascular disease (CVD) were shown to have higher total bilirubin levels than men with CVD (25). Thus, bilirubin may be a novel negative risk factor of CVD (26).

There are few studies, especially prospective ones, regarding the prediction of cardiovascular mortality in the functionally disabled elderly. Our hypothesis was that maybe it is possible that some nontraditional risk factors may outweigh the effect of traditional risk factors in this subgroup of elderly. Biomarkers of inflammation, protein energy wasting and malnutrition are important predictors of cardiovascular mortality in the functionally dependent elderly people. Also, based on the literature, some other ordinary biochemical analyses may accurately predict cardiovascular death in this age group. We chose not to use the established risk scores, but rather to try and build a new one, based on the same or similar biomarkers, which are routinely assessed in biochemical laboratories.

Methods

Study population

The study participants were 253 community dwelling elderly from a pool of 1390 functionally dependent elderly who were using the health care services provided by the Institute for Gerontology and Palliative Care, Belgrade. All the necessary examinations were done during home visits. The participants were aged between 65 and 99 years. The exclusion criteria were absence of a part or an entire extremity (leg or limb amputation due to trauma, congenital, or vascular reasons), totally immobile patients (bed ridden), and presence of carcinoma or some other terminal phase illness. Patients treated with nonsteroidal antiinflammatory drugs, any lipid lowering therapy or corticosteroid medications were also excluded.

Participants gave written consent prior to participation in the study. The study has been approved by the Ethical Committee of the Faculty of Medicine, University of Belgrade.

Measurements

We investigated the traditional risk factors (age, smoking habits, serum lipids, lipid fractions and ratios, blood pressure, anthropometrics), inflammatory markers (white blood cell count, fibrinogen, high sensitivity C-reactive protein) and albumin as the marker of malnutrition. We also considered other

standard biochemical measurements as potential risk factors. Among the 256 subjects originally included, only three had some missing data.

Biochemical measurements were made from fasting blood samples drawn at home on the morning of the baseline examination. All analyses were done routinely in a nationally accredited laboratory. We did not repeat the analyses during the follow-up period. We used the biochemistry analyzer ARCHITECT from Abbot Diagnostics and reagents from the same company. Lipid status was done after 12 hours of fasting with reagents from Abbott Diagnostics (except LDL cholesterol, which was done with BioSystems reagents) on the same analyzer and Adult Treatment Panel III values were used as reference values. Hemoglobin A_{1c} was done using an immunoturbidimetric method with a MULTIGENT HbA_{1c} Reagent Kit from Abbott Diagnostics. Reference value of HbA_{1c} with this method is <6.5%. High sensitivity C-reactive protein (hsCRP) was determined by a latex-enhanced immunoturbidimetric method using reagents from ByoSystems on an Architect biochemistry analyzer (Abbott Diagnostics). The lowest detection limit with this method is 0.06 mg/L and we used the National Academy of Clinical Biochemistry (NACB) 2009 guidelines for the cardiovascular (CV) risk reference value (low risk <1.0 mg/L, average risk 1.0–3.0 mg/L, high risk >3.0 mg/L, very high risk ≥10 mg/L) (27). For the white cell count we used the hematology analyzer ABX-Micros, with the reference interval 4–10×10^9/L. Fibrinogen was done with FIBRINTIMER: Thrombotrack–reference interval 2.0–4.0 g/L.

At inclusion, a standardized interview was performed to assess: medical history, all medications currently used and lifestyle factors (smoking).

Functional status at the time of the interview was assessed using six items (bathing, dressing, toileting, transfer, continence, and feeding) from the Katz ADL Scale (28) and eight items (ability to use telephone, shopping, food preparation, housekeeping, laundry, mode of transportation, responsibility for own medications, ability to handle finances) from the Lawton IADL Scale (29). The level of functional disability was categorized as independent, needs assistance, or dependent (disabled). All participants were having difficulty with one or more IADLs, and having difficulty or needing help with at least one ADL, hence they were all functionally dependent.

Comorbidity information necessary to complete the Charlson Comorbidity Index – CCI (30) was collected from the medical record and supplemented with information from patient interview.

Smoking was classified as current, former (no smoking in the previous 6 months), or nonsmoker. The interviewer then measured height using a ROSS meter with the detection limit of 0.1 cm, weight using the SECA 804 body analyzer scale with the detection limit of 0.1 kg. Waist and hip circumferences were taken

using standard tape with a 0.1 cm detection limit. Blood pressure was measured with a standard mercury sphygmomanometer in patients who were in a sitting position after 15 minutes of rest. BMI was calculated from weight in kilograms divided by height in meters squared.

Patients were followed for a six-month period. We checked medical records for the presence of a new major adverse cardiovascular event (MACE) or cardiovascular death. MACE was defined as self-reported and medically documented myocardial infarction, stroke, and/or aneurism or by-pass surgery. Cardiovascular mortality was defined as mortality from myocardial infarction, heart failure, stroke, aneurism, or complications after vascular surgery.

Statistical analyses

Descriptive statistics for continuous variables are reported as the mean ± standard deviation, or median with interquartile range (IQR). We compared means or proportions for baseline clinical characteristics by Student's t test or Mann-Whitney rank sum test as appropriate (for continuous variables) and x^2 test (for categorical variables) for two groups of participants (participants who survived and others who died during the follow-up period). The associations between mortality risk and different biomarkers were assessed using Cox proportional hazards (PH) regression in time after blood collection, initially for each possible important variable separately and subse-

Table I Selected baseline characteristics of all participants and participants divided in groups by survival status.

Baseline characteristics†	Alive (N=144)	Died from CV diseases (N=109)	All participants (N=253)
Mean (SD) age, years	81.0 (6.0)	82.5 (7.1)	81.6 (6.5)
Gender, female, n (%)	115 (58.1)	83 (41.9)	198 (78.3)
Medical history, n (%)			
CCI (≥3)	37 (25.8)	28 (25.6)	65 (25.5)
ADL disability (≥1)	25 (17.4)	38 (34.9)**	63 (25.5)
IADL disability (≥1)	98 (68.1)	99 (90.8)**	199 (88.0)
Prior MACE	63 (46.3)	73 (53.7)**	136 (53.8)
Lifestyle, n (%)			
Current smoker	10 (6.9)	10 (9.2)	20 (7.9)
Former smoker	34 (23.6)	25 (22.9)	59 (23.3)
Nonsmoker	92 (63.9)	62 (56.9)	154 (60.9)
Physical measurements, mean (SD)			
Systolic BP, mmHg	136 (14)	135 (17)	135 (15)
Diastolic BP, mmHg	77 (8)	76 (9)	77 (9)
Body mass index, kg/m^2	26.7 (5.4)	25.0 (5.0)*	26.0 (5.3)
Laboratory data, mean (SD)			
HsCRP, mg/L	3.66 (5.03)	7.77 (8.13)**	5.42 (6.84)
Fibrinogen, g/L	3.62 (1.10)	4.11 (1.35)**	3.83 (1.23)
Albumin, g/L	41.2 (4.4)	38.5 (5.8)**	40.0 (5.2)
Hemoglobin, g/L	123.6 (11.7)	116.4 (15.0)**	120.5 (13.7)
BUN, mmol/L	6.67 (2.33)	8.62 (4.98)**	7.51 (3.83)
Total bilirubin, μmol/L	11.86 (3.89)	10.16 (3.66)**	11.13 (3.88)
TC, mmol/L	5.80 (1.21)	5.60 (1.27)	5.72 (1.24)
LDL-cholesterol, mmol/L	3.53 (1.05)	3.52 (1.01)	3.53 (1.03)
HDL-cholesterol, mmol/L	1.51 (0.34)	1.42 (0.31)*	1.47 (0.33)
Triglycerides, mmol/L	1.57 (0.74)	1.41 (0.68)	1.50 (0.72)
HbA1c, %	7.00 (2.02)	6.74 (1.70)	6.89 (1.89)

† CCI, Charlson Comorbidity Index; ADL, activities of daily life; IADL, instrumental activities of daily life; MACE, major cardiovascular event (myocardial infarction, stroke and/or peripheral limb amputation due to vascular disease); BP, blood pressure; BUN, blood urea nitrogen; TC, total cholesterol; LDL, low density lipoprotein; HDL, high density lipoprotein; HsCRP, high sensitivity C-reactive protein; HbA1c, hemoglobin A1c; Statistically significant difference died vs. alive group: *P<0.05, **P<0.01.

quently using a multivariable model with only significant variables included. The results are presented as relative risk (RR) and 95% confidence intervals (95% CI). We used cutoff points based on ROC analysis to form dichotomy variables from significant multivariable predictors (31, 32). (Data not shown) Then, we repeated univariate and multivariate Cox PH with these new categorical variables. We used the likelihood ratio statistic to test significance of the addition of each variable separately to a predictive model. Finally, we built the model based on five important predictor variables and validated it internally using a bootstrap technique (33, 34). Participants were then stratified in subgroups by presence of prior major cardiovascular event (MACE). The new score system was tested separately in each subgroup. Differences in Kaplan-Meier survival curves were tested by Log rank test. All analyses were carried out using SPSS software (version 15).

Results

The baseline mean age of participants was 82 years (78% women); 54% had prior MACE and 50% diabetes. During the study (32 months), 109 patients (43.1%) died from cardiovascular diseases. Baseline characteristics of all study participants, participants who have survived and others who died during the follow-up period, are shown in *Table I*. Those who died were older, thinner (P<0.05 for BMI) with frequent history of prior MACE (P<0.01). They also had lower baseline high density lipoprotein (HDL) cholesterol (P<0.05), hemoglobin, albumin and total bilirubin levels (P<0.01) in blood than those who survived, but higher inflammatory markers and blood urea nitrogen (BUN) levels (P<0.01). Significant univariate and multivariate predictors for cardiovascular mortality are shown in *Table II*.

Table II Significant univariate and multivariate predictors of early cardiovascular mortality in Cox proportional hazard regression analysis*.

Variable	Univariate predictors			Multivariate predictors		
	RR	95% CI	P-value	RR	95% CI	P-value
Age	1.03	1.00–1.06	0.067	1.01	0.98–1.04	0.630
Fibrinogen	1.32	1.12–1.56	0.001	1.13	0.95–1.35	0.176
HsCRP	1.05	1.03–1.07	<0.000	1.03	1.01–1.05	0.011
HDL-cholesterol	0.50	0.27–0.92	0.028	0.84	0.44–1.59	0.589
Albumin	0.91	0.87–0.95	<0.000	0.93	0.90–0.97	0.000
Body mass index	0.94	0.90–.99	0.011	0.95	0.91–0.99	0.035
Blood urea nitrogen	1.08	1.05–1.12	<0.000	1.08	1.04–1.12	0.000
Creatinine	1.01	1.00–1.01	0.001	1.00	0.99–1.01	0.456
Bilirubin	0.90	0.85–0.95	0.000	0.91	0.86–0.97	0.004
Hemoglobin	0.97	0.96–0.98	<0.000	1.00	0.98–1.01	0.747
Prior MACE	2.11	1.42–3.14	0.000	2.00	1.34–2.99	0.001

*RR indicates relative risk; CI, confidence interval; HsCRP, high sensitivity C-reactive protein; HDL, high density lipoprotein; Prior MACE, prior major cardiovascular event

Table III Final model based on five important predictors of early cardiovascular mortality in Cox proportional hazard regression analysis.

Variable	Univariate predictors			Multivariate predictors		
	RR	95% CI	*P*-value	RR	95% CI	*P*-value
HsCRP ≥ 2.25 mg/L	2.31	1.56–3.41	<0.001	1.76	1.18–2.64	0.006
Albumin < 40 g/L	2.43	1.63–3.60	<0.001	2.19	1.46–3.30	<0.001
BMI < 25 kg/m^2	1.85	1.27–2.70	0.001	2.01	1.37–2.95	<0.001
BUN ≥ 6.5 mmol/L	1.76	1.20–2.58	0.004	1.74	1.18–2.58	0.006
Bilirubin<10.5 µmol/L	2.10	1.42–3.11	<0.001	1.82	1.22–2.70	0.004

*RR indicates relative risk; CI, confidence interval; HsCRP, high sensitivity C-reactive protein; BMI, body mass index; BUN, blood urea nitrogen
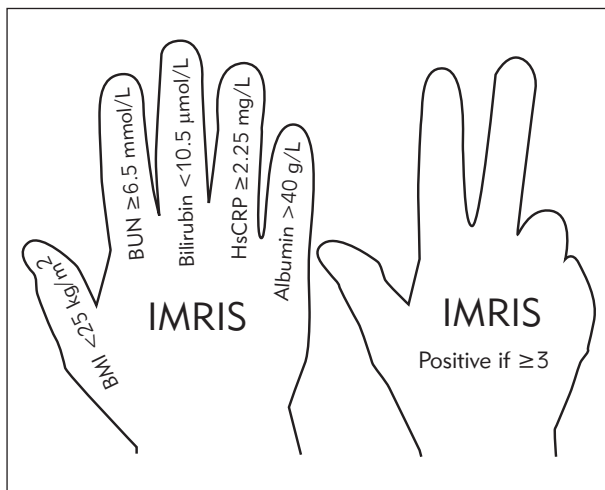
Figure 1 The proposed new inflammatory-malnutrition-renal involved score (IMRIS) – easy to learn and implement in practice (Supplementary material)*

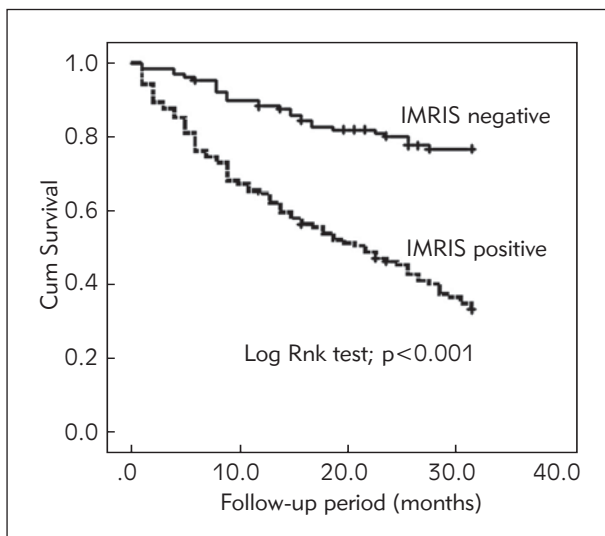*BMI, body mass index; BUN, blood urea nitrogen; HsCRP, high sensitivity C-reactive protein

Figure 2 Kaplan-Meier survival curve in groups with positive and negative inflammatory-malnutrition-renal involved score (IMRIS).

Significant multivariate predictors of cardiovascular mortality were: albumin, BMI, total bilirubin, BUN, and hsCRP. We used cutoff points based on ROC analyses for multivariate predictors to build a significant score, so we included the following predictors: albumin <40 g/L, BMI <25 kg/m^2, total bilirubin <10.5 μmol/L, BUN ≥6.5 mmol/L and hsCRP ≥2.25 mg/L (*Table III*). We did not include prior MACE into the risk score because we wanted our score to be independent of the presence of prior MACE. Our score was informative through the whole spectrum from zero to maximum five scores (Log rank test for trend:
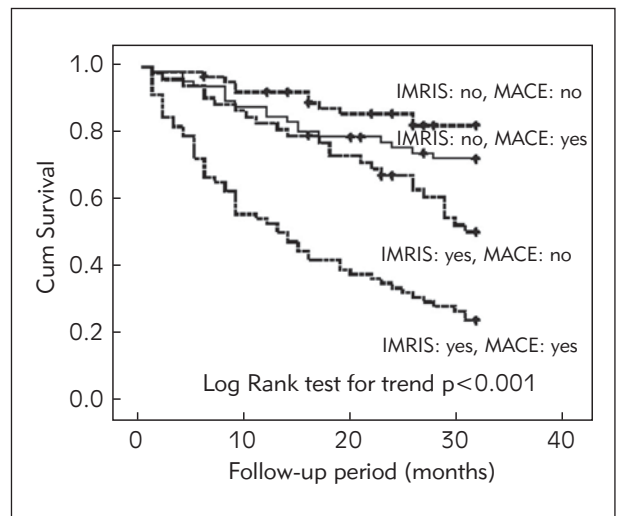

Figure 3 Kaplan – Meier survival curve in groups with positive and negative inflammatory-malnutrition-renal involved score (IMRIS) and with and without a major cardiovascular event (MACE).

χ^2=57.90; P<0.0001), but we decided to split it into two categories: low risk <3, and high risk ≥3. Therefore, the score was positive if someone had three or more of these five predictors positive, and we called it the inflammatory-malnutrition-renal involved score (IMRIS) (*Figure 1*). Cox PH model bootstrapped in 1000 samples and stratified for age, gender and lipid risk factors revealed RR for cardiovascular mortality if someone has a positive IMRIS 3.91 (95%CI: 2.55–5.98), P<0.001. Our model fits the data (Hosmer and Lemeshow test: χ^2=2.435, P=0.487). *Figure 2* shows the Kaplan-Meier curve for positive vs. negative IMRIS (Log rank test χ^2=46.49, P<0.001). The compliance between predicted and actual effect is usually summarized by a few measures and we calculated them. Our score resulted in: sensitivity 73.5% (95%CI: 64.07%–81.40%), specificity 70.1% (95%CI: 61.96%–77.47%), positive likelihood ratio 2.46, negative likelihood ratio 0.38, positive predictive value 65.0%, negative predictive value 77.7% and accuracy 71.5%.

In our participants, the presence of MACE raised the risk of another event two times, RR 2.00 (95%CI: 1.34–2.99), P=0.001. To test the independency of our new score from the presence of MACE, we divided participants into four groups – IMRIS positive vs. IMRIS negative patients with and without MACE. Kaplan–Meier curve shows that IMRIS is a better discriminator for cardiovascular mortality than presence of MACE (*Figure 3*). In a fully adjusted Cox PH multivariate model (adjusted for age, gender, smoking habits, ADL disability, IADL disability, CCI, systolic BP, diastolic BP, lipid profile, waist and hip circumferences), RR for cardiovascular mortality in participants with a positive IMRIS was 4.15 (95%CI: 2.62–6.55, P<0.001), while in the participants with MACE it was 2.12 (95%CI: 1.38–3.25, P=0.001).

Discussion

In our prospective study in the functionally dependent elderly, we found five important risk factors for cardiovascular death. These risk factors were biomarkers of inflammation, malnutrition and renal dysfunction, so we called our score IMRIS (inflammatory-malnutrition-renal involved score).

We can stress that even HDL is not in our score system: it was a significant univariate predictor for cardiovascular mortality and it was the only lipid risk factor that was relevant in our study. We can also notice that our elderly had high mean HDL levels, and maybe it is time to reconsider our reference values for this age group. This demands further investigation in the field of importance to achieve high HDL levels in elderly.

It is not surprising that biomarkers of inflammation are within our score, when we know that chronic inflammation is considered to be an underlying mechanism of ageing and age-related diseases (35, 36). Moreover, in previous studies, the effects of inflammatory mediators upon survival were separate from preexisting morbidity and other traditional risk factors for death. Clarke et al. found that higher CRP and lower albumin levels strongly predicted both vascular and non-vascular mortality in older men, irrespectively of other characteristics (24). Jenny et al. (37) found that CRP and fibrinogen were more strongly associated with death in older men than women, and more strongly associated with early than late death. In the MONICA/KORA Study, initially healthy men with baseline hsCRP concentrations >3 mg/L had a 2-fold increase in risk of total mortality (seven years follow-up) and the risk was most prominent for cardiovascular mortality (38–40). The POLA Study group found that the risk for early death in healthy elderly men was increased for high CRP and for low albumin. Prediction of early death was enhanced by the joint effect of these two markers. For late death, the only significant association was with CRP in men. In women, neither CRP, nor albumin was associated with early or late death (41). In our study, we did not find sex-related differences. On the contrary, women were the predominant gender (78.3%), but we still found that both high hsCRP and low albumin were predictive of early cardiovascular death.

Djoussé et al. (42) examined in the prospective Framingham Offspring Study whether low serum albumin is associated with greater risk for myocardial infarction and all-cause mortality. They concluded that lower serum albumin concentrations are associated with an increased risk of coronary disease in both sexes and with all-cause mortality in women. It was not clear if that is an independent effect of albumin, or low albumin only reflects inflammation. Albumin per se has antioxidant properties, inhibits lipid peroxidation systems and may inhibit endothelial apoptosis (41). Also, it is possible that biomarkers of inflammation (increased levels of CRP and decreased levels of albumin) reflect a final common biochemical pathway of devastating health status which is a predisposition to vascular and non-vascular mortality in old age (24).

The relationship between obesity, inflammation and cardiovascular disease is more complex than we usually think. The acute phase proteins when they are at high levels exert a marked influence on the nutritional status, as they determine anorexia and weight loss through decreased protein catabolism and anabolism (44). In contrast with middle-aged initially healthy individuals, where obesity is a strong cardiovascular risk factor, an »obesity paradox« exists among patients with multiple risk factors and a history of cardiovascular disease (45, 46). Weiss et al. (47) retrospectively evaluated the relationship between BMI and long-term mortality in very elderly subjects who were hospitalized in an acute geriatric ward. Patients with the lowest BMI had the highest rate of mortality even after excluding subjects who died within 6 months of hospitalization and BMI was inversely associated with mortality regardless of sex and cause of death. In our study, BMI <25 kg/m^2 was predictive of cardiovascular death regardless of sex too, and we incorporated it in our risk score.

Elevated BUN has been associated with adverse outcomes and has been already incorporated into myocardial infarction risk prediction models. BUN level is particularly important in elderly people because creatinine may weaken its ability to reflect changes in glomerular filtration rates as muscle mass decreases (48). It was exactly the evidence in our study, because creatinine was not a multivariate predictor of cardiovascular mortality, but BUN was incorporated in our score. In a large retrospective cohort of Medicare patients (aged 65 years), increased 1-year mortality risk was found with a serum urea nitrogen (SUN) level greater than 6.1 mmol/L in patients who experienced a myocardial infarction, and with a SUN level greater than 5.7 mmol/L in patients who experienced heart failure (49). In the abovementioned study, there was not a single cut point for SUN level to predict mortality risk, because the incremental risks across the whole spectrum were informative. This was in agreement with our results, where BUN 6.5 mmol/L was incorporated in the mortality risk score.

Bilirubin is a major physiologic antioxidant cytoprotectant. As an antioxidant, bilirubin demonstrated antiatherogenic function through inhibition of LDL oxidation and through inhibition of vascular endothelial activation (50). Several epidemiological studies have found that bilirubin levels are inversely associated with coronary heart disease (51, 52). In the National Health and Nutrition Examination Survey, increased serum total bilirubin levels were associated with reduced peripheral arterial disease and stroke prevalence (53, 54). In a prospective study in Korean men and women, low serum bilirubin levels were

associated with an increased risk of stroke incidence (55). In our study, the total serum bilirubin <10.5 μmol/L was predictive of cardiovascular death and was also a part of the new scoring system.

Our study has several limitations. First, the study was done on a small number of functionally dependent elderly in one city (Belgrade). It is necessary to retest elderly in large multiethnic cohorts. Furthermore, we followed our participants for only 32 months. It means that we do not know if the same risk factors would be significant for a longer period of time. Also, we did not repeat the biochemical markers during the follow-up period. It would be of particular importance to see how they would change, and if there would be any change at all.

Conclusion

Results of our study revealed five important risk factors for cardiovascular death in functionally dependent elderly and we successfully incorporated them in a new risk score named IMRIS. Our results are in consistency with other studies performed in this age group. Nevertheless, these preliminary findings require further validation in a separate cohort of elderly. These measurements are routine ones, so it is not necessary to have some additional charges. This risk score provides an opportunity to improve progno-sis by targeting these five predictors (for example, targeting individualized nutrition or hydration, or therapy with 20% human albumin), but only after we confirm its accuracy.

Authors' contribution

Vasović O: Data collection, analysis/interpretation, statistics, concept/design, drafting article, critical revision of article, approval of article; Lalić K: concept/design, critical revision of article, approval of article; Trifunović D: concept/design, statistics, drafting article, approval of article; Milić N: analysis and interpretation of data, statistics, approval of article; Jevremović I, Popović LJ, Paspalj D, Kalasić Milićević A, Ševo G, Despotović N, Erceg P, Milošević DP: concept/design, critical revision of article, approval of article.

Conflict of interest statement

The authors stated that there are no conflicts of interest regarding the publication of this article.

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