ORIGINAL ARTICLE

Evaluation of biochemical markers effectiveness in elderly malnutrition assessment

Larisa Gavran[1], Jelena Pavlović[2], Maja Račić[3], Nedeljka Ivković[4], Ksenija Tušek Bunc[5]

[1]Department of Family Medicine, School of Medicine, University of Zenica, [2]Department of Nursing, School of Medicine, University of East Sarajevo, [3]Department of Primary Health Care and Public Health, School of Medicine, University of East Sarajevo, [4]Department of Oral Rehabilitation, School of Medicine, University of East Sarajevo; Bosnia and Herzegovina, [5]Department for Public Health School of Medicine, University of Maribor, Slovenia

ABSTRACT

Aim To systematically review the scientific evidence of biomarker validity, reliability, specificity and sensitivity in identifying malnutrition in the elderly.

Methods Peer-reviewed journals were searched using PUBMED and EBSCO from January 1998 to April 2018. The articles included description of the association between malnutrition blood biomarkers and validated nutritional status assessment instruments and studies were conducted among community-dwelling elderly or nursing home residents.

Results The research strategy identified a total of 293 studies. This literature review picked out seven articles for follow-up evaluation. A total of sixteen blood biomarkers were identified. Six studies found a significant association between the nutritional assessment score and albumin level.

Conclusion Combining serum concentrations of malnutrition biomarkers with nutritional status assessment tools has a great potential in identifying the risk of malnutrition in the elderly, while also increasing sensitivity and specificity.

Keywords: aged, biomarkers, geriatric assessment, humans, malnutrition

Corresponding author:
Jelena Pavlović
Department of Nursing,
School of Medicine of Foča,
University of East Sarajevo
Studentska 5, 73 300 Foča,
Bosnia and Herzegovina
Phone: +387 58 210 420;
Fax: +387 58 210 007;
E-mail: pjelena551@gmail.com
ORCID ID: https://ordic.org/0000-0002-8591-4316

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INTRODUCTION

Good nutrition is a fundamental component of health, independence and quality of life of elderly persons (1). Malnutrition may cause health problems such as the increased risk of morbidity (chronic diseases, pathological fractures, impaired wound healing, slow post-operative recovery, development of decubitus ulcers, weakened functionality, lack of appetite), and increased hospitalization rate, number of hospital treatment days and mortality rate (2). Studies have shown that the prevalence of malnutrition after the age of 65 has been on the rise reaching a range of between 15-85% (2-4). According to Bedogni et al. (5), nutritional status is a result of the interaction of three variables: food ingestion, absorption, and the use of nutrients. It clearly follows from the described definition that an ideal nutritional status assessment and malnutrition screening instrument should include the assessment of dietary, anthropometric, functional indicators, and laboratory biomarkers in the blood (Figure 1) (5,6). A recent systematic review has shown that multiple biochemical parameters (albumin, prealbumin, hemoglobin, total cholesterol, and total protein) may be used in diagnosing malnutrition in the elderly (7). However, it remains unknown which are the reference cut-off values of these biomarker blood parameters, and which biomarker is usable, precise and reproducible, acceptable to the patient, easy for clinical interpretation, and cost-effective, while having the high sensitivity and specificity necessary for the expected outcome. Such a biomarker would have a promising potential for the malnutrition diagnosing system.

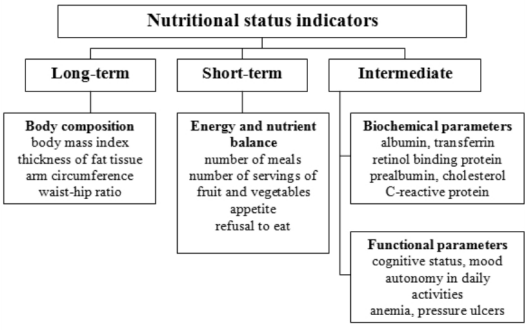

Figure 1. Definition of nutritional status indicators

The aim of this systematic review was to study, investigate, analyse, and synthetize the scientific evidence of biomarker validity, reliability, specificity and sensitivity in identifying malnutrition in elderly patients.

MATERIALS AND METHODS

Study design

The systematic literature overview was made according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (8).

We considered observational, longitudinal, retrospective, and cross-sectional studies that reported an association between blood biomarkers levels and validated nutrition assessment instruments, such as anthropometric measurements (body mass index – BMI, or skinfold thickness). Additionally, it followed screening questionnaires: Mini Nutrition Assessment-Short Form (MNA-SF), Malnutrition Universal Screening Tool (MUST), Nutritional Risk Screening 2002 (NRS-2002), Geriatric Nutritional Risk Index (GNRI), Nutritional Risk Index (NRI), Instant Nutritional Assessment (INA), Nutrition Screening Initiative (NSI), Short Nutritional Assessment Questionnaire (SNAQ), Subjective Global Assessment (SGA), and the Nutritional Risk Screening Tool (NRST). Inclusion criteria were studies conducted among community-dwelling elderly and/or nursing home residents. Country and English-language restrictions were not applied. Outcomes of interest were the sensitivity and specificity of blood biomarkers, as well as their ability to identify malnutrition risk among the elderly (Table 1).

Table 1. Study inclusion and exclusion criteria

Variable	Inclusion criteria	Exclusion criteria
Population	People over the age of 60, well-oriented in time and space, without malign diseases, dementia, chronic renal insufficiency	People under the age of 60, persons with dementia, persons with malign diseases and with chronic renal insufficiency
Environment	People living in community or in gerontology institution	People in hospital environment
Study type	Observational, longitudinal, retrospective, transversal	Non-empirical studies
Outcome	Identification of biochemical malnutrition markers	Non-identification of biochemical malnutrition markers
Development and validation	Described	Not described
Other	Abstract availability, year of publication from1998, full text available	Abstract and full text unavailability, year of publication before 1998

Methods

Malnutrition was defined as deficiency or imbalances in an intake of energy and macro/micro nutrients (5). The studies were downloaded via the electronic databases PUBMED and EBSCO, and by manual search of relevant studies from a list of reference key articles. The electronic databases were searched from the period January 1998 to April 30 2018 by defining key words adapted for each database (malnutrition, nutrition, blood markers, serum, elderly), and words from MESH (Medical Subject Headings) and Boolean operators, AND/OR words establishing a logical connection with the paper search concepts at Medline. There was an advanced search modality. The manual search of original papers, looking for additional acceptable studies, was conducted through the Electronic Journals Library. Papers were searched through various journals (Nutrition, The American Journal of Clinical Nutrition, Nutrients, Nutrition Reviews, Journal of Nutrition, and European Journal of Clinical Nutrition). Titles and abstracts were reviewed and, if an abstract met the inclusion criteria, the full text was downloaded. In accordance with the search criteria, the full texts of papers selected were independently assessed by two investigators and, in case of any doubt before the final decision, the investigators sought a third investigator's opinion.

During this step, the application of the final criteria for inclusion of papers into the analysis resulted in the selection of biomarker research studies with validated instruments in identifying malnutrition in persons over 60 years of age. The data from each paper using a data extrapolation form based on the Best Evidence Medical Education (BEME) coding sheet (9) were pulled out. After investigators checked the extrapolated data, they focused on biochemical markers, study methodology, and results. No exact meta-analysis could be done due to discrepancy between the methods used, the different statistical analyses of the studies included in the final analysis, the difference in measurement outcomes, different biomarker validity values in relation to the instruments used, as well as the lack of reliable borderline values of biomarkers for elderly persons. The synthesis showed the ability of blood biomarkers in identifying an elderly individual with malnutrition or at high risk of malnutrition. The extrapolated data are presented in a tabular form in order to facilitate comparison. Each study included the name of author(s), publication year, sample size, study design, methodology, identified biochemical markers, and results (Table 2).

RESULTS

The research strategy identified a total of 293 studies. Following data deduplication and selection of papers based on titles and abstracts, a total of 277 papers were excluded because they were not focused on malnutrition, the population was under the age of 60, the authors did not use laboratory analysis to identify malnutrition, or the studies did not undergo a validation process. Nine of the remaining studies were included for a full text review, of which 7 were selected for extrapolation and final analysis (Figure 2).

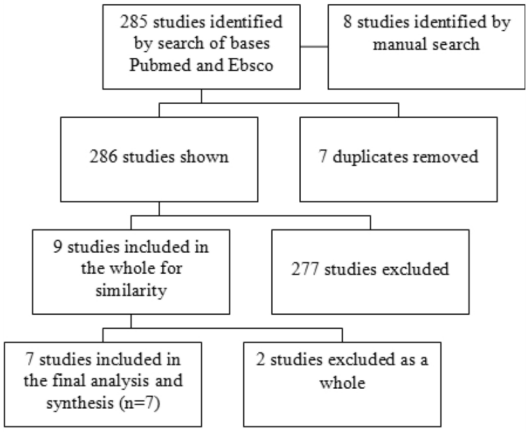

Figure 2. Flow diagram of the research and selection process

Sixteen biomarkers were identified in the literature review. Most commonly analysed were albumin and total cholesterol. Other biomarkers found were lymphocyte count, leucocytes, haemoglobin, prealbumin, triglycerides, zinc, copper, transthyretin, leptin, orosomucoid, insulin-like growth factor-1 (IGF-1), IGF binding protein-1 (IGFBP-1), and C-reactive protein (CRP).

The biomarkers values were evaluated against GNRI (10) , NRST (11), MNA (12,13) , SGA (13,14), MNA-SF/NRS2010 (15), and antropometric measurements (BMI and skinfold thickness) (16).

Biochemical concentrations were measured using well-accepted methods, with variations depending on the setting. Three studies detected a significant, positive correlation between nutritional assessment and albumin level (10-12) and, in

Table 2. Identified biochemical markers for the evaluation of nutritional status in the elderly

Author, year (sample size, n)	Design study	Instrument	Marker	The result
Abd-El-Gawad, et al.10, 2004 (n = 131)	Prospective cohort study	Anthropometric measurements GNRI	Total protein Lymphocytes Haemoglobin Albumin Total protein Prealbumin Total cholesterol Triglycerides Zinc Copper	**Average values of biomarkers in malnutrition (GNRI score)** WBCs (103/cm): 8.56 ±6.21; p=0.448; Lymphocytes: 1.55±0.67; p=0.637; Haemoglobin (g/dL): 10.95 ± 3.01; p=0.026; Total protein (g/dL)- 6.39 ± 0.78; p=0.243; Albumin (g/dL): 2.66 ±0.46; p<0.001; Prealbumin (mg/dL):-6 (3-10) ; p=0.902; Total cholesterol (mg/dL): 142.1±.74.2, p=0.213; Triglycerides (mg/dL): 79 (57-107) ; p=0.882; Zinc: 93.76 ± 17.59; p=0.882; Copper : 117.12 ±22.45; p=0.154; **Correlations between GNRI and biomarkers values** Total protein: r=0.161; p=0.557; Lymphocytes: r=0.093; p=0.157; Haemoglobin: r=0.052; p=0557; Albumin: r=0.463; p<0.001; Prealbumin: r= -0.110; p=0.212; Total cholesterol: r=0.128; p=0.171; Triglycerides: r=0.004; p=0.965; Zinc: r=0.004; p=0.965;
Htun NC, et al.11, 2015 (n = 1921)	Prospective cohort study	Anthropometric measurements NRST GNRI MNA-SF	Cholesterol Albumin	**Correlations between NRST and biomarkers** Total cholesterol (mg/dL): r=0.057; p=0.012; Serum albumin (g/dL): r=0.094; p<0.001
Kuzuya M, et al.12, 2005 (n = 226)	Cross section study	Anthropometric measurements MNA MNA-SF	Albumin Cholesterol Lymphocytes	**Correlation between MNA score and biomarkets** Total cholesterol r=0.36; p<0.001; Albumin r=0.60; p<0.001; Lymphocytes r=0.01; p=0.935 Sensitivity of malnutrition (MNA cutoff point <17) for hypoalbuminemia (<3.5 g /dL)- 0.810 Specificity of malnutrition (MNA cutoff point <17) for hypoalbuminemia (<3.5 g /dL)-0.860 Sensitivity of malnutrition (MNA cutoff point <17) for hypocholesterolemia (<150 mg/dL) 0.786 Specificity of malnutrition (MNA cutoff point <17) for hypocholesterolemia (<150 mg/dL) 0.822
Christensson L, et al.13, 2002 (n = 261)	Cross section study	Anthropometric measurements SGA MNA	Albumin Transthyretin	**SGA class and serum proteins levels** Transthyretin (g/l): 0.24±0.06 (well-nourished), 0.22±0.06 (moderate), 0.19±0.06 (severe malnutrition) Albumin (g/ L): 35.0±5.0 (well-nourished), 4.0±5.0 (moderate), 31.0±6.0 (severe malnutrition) **MNA class and serum proteins levels** Transthyretin (g/L): 0.24±0.06 (well-nourished), 0.23±0.06 (risk), 0.19±0.06 (malnourished) Albumin (g/ L): 35.8±4.5(well-nourished), 34.5±5.0(risk), 30.2±5.6 (malnourished)

Kuyuza M, et al.14, 2007 (n = 262)	Cross section study	Anthropometric measurements SGA ADL	Albumin	**Validity of cutoff point of serum albumin for malnutritional markers.** Well-nourished individuals (SGA) 22.8 % had albumin <35 g/ L; specificity 0.772 Moderately malnourished individuals (SGA) 64.0 % had albumin <35 g/ L, severely malnourished individuals (SGA) 78.9 % had albumin <35 g/ L; sensitivity-0.783
Zhou J, et al.15, 2015 (n=142)	Cross section study	MNA-SF NRS 2002 Anthropometric measurements	Haemoglobin Total lymphocyte count Albumin	The cutoff value for albumin was set at 35 g/L as an indicator of under-nourished. The cutoff value for total lymphocyte count (TLC) was<2.0×103/mm3 for both genders Haemoglobin (Hb) was compared with reference values for males (120 g/L) and females (110 g/L), respectively. **Difference between (well-nourished) and malnourished individuals** **NRS** Albumin: 41±6.73 (normal), 38.21±6.34 (malnourished) ; p=0.01; Hb: 132.93±16.66 (normal), 121.39±23.57 (malnourished) ; p=0.0008; TLC: 1.71±0.77(normal), 1.70±0.67(malnourished) ; p=0.94; **MNA-SF** Albumin: 41.82±6.47 (normal), 37.81±6.38 (malnourished) ; p=0.0003; Hb: 133.86±17.98 (normal), 122.06±21.18 (malnourished) ; p=0.004; TLC: 1.74±0.71 (normal), 1.66±0.76 (malnourished) ; p=0.52;
Bouillanne O, et al.16 , 2007 (n=192)	Observational prospective study	Anthropometric measurements BMI Skinfold thickness	Albumin, Transthyretin, Leptin, Insulin-like growth factor-1 (IGF-1), IGF binding protein-1 (IGFBP-1), C-reactive protein (CRP), Orosomucoid	Leptin (cutoff 4 mg/L in men): sensitivity: 0.89; specificity: 0.82 Leptin (cutoff 6.48 mg/L in women): sensitivity 0.90; specificity 0.83. **Univariate correlation between serum leptin and other biomarkers** Albumin (g/l): r=0.110 F; r=0.423 M; p>0.05; Transthyretin (mg/l) : r=0.194F; r=0.364 M; p>0.05; CRP (mg/L): r=0.017 F; r=0.039 M; p>0.05; Orosomucoid (g/l) r=0.031 F; r=0.046 M; p>0.05; IGF-1 (mg/L): r=0.198 F; r=0.534 M; p>0.05; IGFBP-1 (mg/L): r=0.425 F; r=0.708 M; p<0.0005; IGFBP-3 (mg/L): r=0.152 M; r=0.329 M; p>0.05;

ADL, Katz index of independence in activities of daily living; CRP, C-reactive protein; GNRI, Geriatric Nutritional Risk Index; IGF-1, Insulin-like growth factor-1; IGFBP-1, IGF binding protein-1; MNA, Mini Nutritional Assessment; MNA-SF, Mini Nutritional Assessment-Short Form; NRST, Nutritional risk screening; NRS2002, Nutritional Risk Screening 2002; SGA,: Subjective Global Assessment; WBC, white blood cells

three studies, individuals with albumin <35 g/L had higher scores for malnutrition compared to individuals without hypoalbuminemia (13-15). Two out of three studies analysing cholesterol level detected a correlation between malnutrition and hypocholesterolemia (11,12). The assessed level of haemoglobin (<13g/dL) for the given population was relatively low, even among those characterized as malnutrition risk-free (15). Total lymphocyte count was not significantly associated with malnutrition categories (10,12,15). Transthyretin level was significantly lower among malnourished elderly compared to those who were well-nourished or at risk for malnutrition (13). Leptin concentration was highly correlated with the anthropometric data used to define nutritional status (16).

Overall, the quality of included studies was low to moderate.

DISCUSSION

The analysis and synthesis of the reviewed studies showed that the nutritional status assessment plays an important role in persons older than 65. Blood biomarkers, particularly albumin, haemoglobin and cholesterol, are useful biochemical indicators of malnutrition (17). Protein albumin was the most frequently cited biochemical marker and the most frequently studied malnutrition-diagnosing protein used in the relevant studies (17). Previous research analysed the effect of serum albumin concentrations on disease outcomes and discovered that these are associated with increased morbidity and mortality (17). The relevant studies defined borderline haemoglobin values at 13.5 – 17.5 g/dL for male and 12.0 – 15.5 g/dL for female (17). Serum haemoglobin concentrations were relatively low, even among those at risk of malnutrition (<14.2 g/dL), while serum cholesterol concentrations <160 mg/dL (hypocholesterolemia) were frequently associated with malnutrition (18). It should be also noted that borderline total protein value of <6 g/dL is inadequate for the diagnosis of malnutrition or may cause a misdiagnosis when using MNA and SGA instruments (19). Total MNA score showed a good correlation with albumin and total cholesterol, as well as high specificity in lower values of both albumin <3.5 g/dL and cholesterol <150 mg/dL suggesting that albumin and cholesterol represent reliable malnutrition markers (12). It is well known that serum albumin and cholesterol concentrations drop with aging (18). In addition, GNRI components, serum albumin, and loss of weight are correlated with morbidity and mortality in numerous studies (20,21). Relevant international validation studies have shown a total cholesterol level of 3.88 mmol/L, in accordance with the Subjective Global Assessment (SGA), indicating high specificity, but low sensitivity as a malnutrition indicator (21). This could cause misidentification of persons at risk of malnutrition, meaning that the reference borderline values of those biomarkers are not reliable in elderly persons (12). Serum albumin is the most useful tool for assessing and monitoring long-term changes in nutritional status, while its value has a predictive value in hospitalized patients (22,23). On the other hand, hypoalbuminemia may be a result of underlying disease (hepatic insufficiency, infection, heart insufficiency, burns, trauma, or the significant loss of fluids) (12). Due to long plasma half-life, albumin shows a minimal response to short-term fasting or nutritional support (22). Prealbumin, on the other hand, due to its short plasma half-life, more accurately shows short-term changes in nutritional status (22). Haemoglobin is not a true indicator of inflammation, but has low values in patients with malnutrition or inflammation. A low level of haemoglobin, in the absence of iron, folic acid or vitamin B12 deficiency, and in the absence of haematological disease, indicates the existence of inflammation and/or low body mass (11).

The most important step prior to clinical use of any biomarker is the accurate definition of reference values of relevant markers and precise interpretation of haematological test results, although it is well known that blood biomarker concentrations often vary with age, gender, race, metabolism, diet, and even overall health status. It is necessary to clearly define the reference cut-off values of those parameters, and to determine which biochemical marker can be clinically usable, precise and reproducible, acceptable to the patient, easy for clinical interpretation, while having a high sensitivity and high specificity for the expected outcome, as well as promising potential in the recommended malnutrition diagnosing system. Due to the difficulties in defi-

ning reference values for individual parameters, it is neither simple nor easy to select a nutritional status assessment method. Those difficulties result from major individual and population differences which take place during senium. Due to the absence of a universally accepted definition of malnutrition and a "gold standard" for diagnosing malnutrition, a comprehensive nutritional status assessment requires choosing a simple tool with all three nutritional status indicators, one which has sufficient sensitivity and specificity. This will enable timely malnutrition identification, as well as the treatment of elderly persons with malnutrition.

Combining biochemical markers and validated malnutrition assessment tools increases specificity and sensitivity. Two studies combined a validated screening tool and/or a blood biomarker in order to minimize malnutrition risk (24), while multiple studies combined one or more blood biomarkers and anthropometric malnutrition identification measurements (25-27). Dietary tools combining anthropometric measurements, biochemical markers, and a GNRI instrument have also been proposed for assessing malnutrition. However, none of the proposed tools have been reliably validated. Validity studies are necessary before those dietary indicators are recommended in the assessment of malnutrition in the elderly (28).

There are several limitations of the study. The literature search required a good knowledge of the research subject and the journals in which relevant studies might have been published. Manual search increased the number of papers reviewed, but was subjective (the references chosen in key articles). Numerous studies were based on a relatively narrow sample size, so the results obtained cannot be generalized for this population. Dietary input assessed by a three-day food record was yet another limitation of the studies included for systematic review. Food intake assessment differed between studies, making the comparison of results unclear and unmeasurable. Certain tools had a low Cronbach's alpha value, which can be a major deficiency in terms of reliability analysis. Most of the studies conducted were of poor methodological quality. There were differences in data collection methodology and methods, so no reliability was expected in individual instruments. Some authors relied on dietary changes and weight loss data, perhaps leading to erroneous analyses. The studies included showed liver protein albumin as the most commonly studied malnutrition diagnosing protein, followed by prealbumin, cholesterol, haemoglobin, and total protein, with an evident lack of any study assessing other blood biomarkers. Therefore, statistical power may be limited.

In conclusion, leptin, albumin, haemoglobin and total cholesterol are useful biochemical malnutrition indicators in elderly persons. Combining malnutrition biomarkers with nutritional status assessment tools has a greater potential in identifying the risk of developing malnutrition in the given population, while increasing sensitivity and specificity. It is necessary to update which reference biomarker values are reliable for a malnutrition assessment of elderly persons. Due to the absence of a universally accepted diagnostic definition, it is necessary to choose a simple, sensitive and specific tool, one which can be operationally adapted and useful for a nutritional status assessment. For the purpose of early malnutrition detection, additional, randomized studies are necessary focusing on a comprehensive nutritional status assessment.

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Conflicts of interest: None to declare.

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