

Article

# Impact of malnutrition on long-term mortality in elderly patients with acute myocardial infarction

Running head: Malnutrition in elderly patients with acute myocardial infarction.

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**Abstract:** Background: Malnutrition is a frequent condition in the elderly and is associated with prolonged hospitalization and increased mortality. However, the impact of malnutrition among elderly patients with acute myocardial infarction has not been clarified yet. Methods and Results: We have enrolled 174 patients aged 65 years and over, admitted with the diagnosis of acute myocardial infarction (AMI) who underwent to the evaluation of nutritional status by Mini Nutritional Assessment (MNA) and of mortality risk by Grace score 2.0. All-cause mortality was the outcome considered for this study. Over a mean follow-up of 24.5±18.2 months, 43 deaths have been registered (24.3%). Non-survivors were more likely to be older, with worse GFR, lower SBP, lower albumin and MNA score, higher prevalence of Killip classification III-IV grade, and higher Troponin I levels. Multivariate Cox proportional analysis revealed that Grace score and MNA showed a significant and independent impact on mortality, (HR=1.76, 95% CI=1.34-2.32 and HR=0.56, 95% CI=0.42-0.73, respectively). Moreover, the clinical decision curve revealed a higher clinical net benefit when the MNA was included compared to the partial models without MNA. Conclusions: Nutritional status is an independent predictor of long-term mortality among elderly patients with AMI. MNA score in elderly patients with AMI may help prognostic stratification and identification of patients with/at risk of malnutrition in order to apply interventions to improve nutritional status and maybe survival in this population.

**Keywords:** mini nutritional assessment, acute myocardial infarction, mortality, elderly.

## 1. Introduction

Malnutrition is a common condition in the elderly with an overall prevalence higher than 20% [1]. Physical deconditioning, cognitive impairment and comorbidities together with other components of patho-physiological aging such as: dysphagia, malabsorption and derangement of hormonal systems lead to an imbalance of anabolic-catabolic metabolism that translates in malnutrition [2]. The Mini Nutritional Assessment (MNA) is a validated test recommended for

nutritional screening in the geriatric population and is widely used in different clinical settings including: acute care, rehabilitation, nursing home and community [3]. Malnutrition has been associated with impaired cardio-respiratory performance, increased risk of falls, prolonged hospitalization and increased mortality [4-6]. Importantly, nutritional status evaluated by MNA scale has been demonstrated to predict mortality in general free-living population [7]. The prevalence and the severity of coronary vascular disease increase with age and more than 35% of patients with Acute Myocardial Infarction (AMI) are  $\geq 75$  years old [8-9]. The Grace risk score 2.0 algorithm estimates the short and long-term mortality risk in acute coronary syndromes (ACS), and it is mainly based on a variety of cardiovascular parameters such as heart rate, systolic blood pressure, electrocardiography modifications, cardiac ischemia biomarkers and cardiogenic shock [10].

Recent studies have reported that low body mass index (BMI) and hypoalbuminemia are important risk factors for mortality in elderly patients after ACS [11-12]. Furthermore, evaluation of nutritional status by body weight and albumin level has demonstrated to influence clinical outcomes during hospitalization in patients with myocardial infarction [13]. However, the evaluation of nutritional status with a validated geriatric screening test in a population of elderly patients with AMI, and its impact on the long term prognosis of these patients is poorly studied. Accordingly, the aim of the present study has been to evaluate the impact of nutritional status evaluated by MNA on long-term survival in a population of elderly patients with AMI.

## 2. Materials and Methods

### 2.1 Study population:

All patients aged 65 years and older admitted at the Intensive Coronary Care Unit (ICCU) of the University of Naples Federico II, with the diagnosis of AMI were screened for inclusion in this study. Inclusion criteria were: a) diagnosis of ST elevated myocardial infarction (STEMI) or non ST elevated myocardial infarction (NSTEMI) b) age  $\geq 65$  years c) willingness to participate in this study. Patients underwent a complete clinical examination and a structured interview about cardiovascular risk factors and other comorbidities. Based on clinical evaluation, Killip classification was also determined. Baseline laboratory, echocardiography and angiography findings including: white blood cells, hemoglobin, troponin I, creatine kinase MB isoenzymes, albumin, serum creatinine levels to estimate glomerular filtration rate (GFR), left ventricular ejection fraction (LVEF), severity of CAD and primary coronary intervention (PCI) were recorded. Grace risk score 2.0 for mortality was calculated based on age, heart rate, systolic blood pressure, creatinine and troponin level, Killip Class, ST segment modifications and cardiac arrest, as previously described [14]. The study has been approved by the Local Ethical Committee and all patients were informed and signed a written consent to participate to this study.

### 2.2. Diagnosis of AMI

AMI has been diagnosed according to the third universal definition of myocardial infarction criteria recommend by European Society of Cardiology, the American Heart Association and WHO [15-16]. The diagnostic criteria were as follows: a) typical chest pain, upper extremity, mandibular or epigastric discomfort of more than 20 minutes, b) ST depression  $\geq 0,05$  mV in at least two contiguous leads and or T wave inversion  $\geq 0,1$  mV in at least two contiguous leads with R/S ratio  $> 1$ ; ST elevation at the J point  $\geq 0,1$  mV in two contiguous leads except V2-V3  $\geq 0,2$  mV in men  $> 40$  years and  $\geq 0,15$  mV in women c) serum troponin I or creatine kinase levels above the 99th percentile of the normal reference population during the first 24 h after admission.

### 2.3 MNA:

Nutritional status was assessed with the complete MNA administered from a clinical researcher after the angiography or revascularization procedures. MNA consists of 18 items: measurements of BMI, calf and mid-arm circumference, questions on food and beverages intake, weight loss, acute disease, mobility, psychological stress, depression, dementia, independently living, poly-pharmacy,

pressure injuries and self view of nutritional and general clinical status. It has been reported that a score  $\geq 24$  identifies a condition of normal nutrition, a score  $\geq 17$  and  $\leq 23.5$  a condition of malnutrition risk, and a score  $< 17$  indicates malnutrition [17].

*2.4 Follow-up:*

All-cause mortality was the outcome considered for this study. The patients were contacted by telephone to determine their survival status. Follow-up period was termed at the end of the study period (May 2017) or in the case of death.

*2.5 Statistical analysis:*

Continuous variables are expressed as mean  $\pm$  standard deviation (SD) and compared by the use of Student's *t* test. Categorical variables are expressed as proportion and compared by use of  $\chi^2$  test. The Cox proportional hazard analysis was used to identify the factors associated with all-cause mortality. Considering that Grace Score includes multiple cardiovascular parameters and using parsimonious criteria, we tested in the cox model the following, as potential variables associated with mortality: age, gender, BMI, LVEF, Grace Score, Diabetes Mellitus, albumin level and MNA score. To determine the contribution of each variable to the global outcome, the partial contribution of each variable to the global  $R^2$ , has been measured. The decision curve analysis [18], a suitable method to test alternative prognostic strategies was used to estimate the potential additive clinical value of MNA evaluation. With this method, the net benefit obtained using in the clinical setting a given prognostic model is compared to the other 2 possible alternatives, i.e. the "treat all" and "treat none" strategies.

To have a comprehensive view of the relative weight of each factor on the survival curve, the Hazard Ratio (HR) of the significant continuous variables included in the final Cox models were related to one Standard Deviation (SD) variation for both MNA and Grace mean Score. Directly adjusted survival plots [19] obtained by averaging the Cox survival curves adjusted by the covariate values of each subject are used to compare the survivals at specific factors' values to the overall Kaplan–Meier. Data were analyzed by Stata version 13.0 (StataCorp LP, College Station, Texas). Statistical significance was accepted at  $P \leq 0.05$ .

**3. Results**

*3.1 Patient characteristics:*

The final study population consisted of 174 patients, with a mean age of  $74.26 \pm 7.08$  years, 65.0% were males (114/174), with a mean LVEF of  $39.89 \pm 8.49\%$ ; 52.9% had STEMI, mean Grace score was of  $150.01 \pm 24.38$ . Demographic data of the overall study population and sorted in survival and non-survival are reported in Table 1. Interestingly, no differences have been observed between survivors and non-survivors in gender, BMI, presence of DM, COPD, hypertension, heart rate, hemoglobin and glycaemia level. However, non-survivors were more likely to be older, with worse GFR (at the edge of the significant threshold; respectively  $p = 0.078$ ;  $0.080$ ), lower SBP, lower albumin and MNA score, higher prevalence of Killip classification III-IV, and higher Troponin I levels. Based on MNA score, 14.4% (25/174) patients were malnourished ( $MNA \leq 17$ ), 35.6% (62/174) were at risk for malnutrition ( $MNA > 17$  and  $\leq 23.5$ ) and 49.4% (86/174) presented a good nutritional status ( $MNA > 23.5$ ). A significant ( $p \leq 0.001$ ) proportion of non-survivals 72.1% (31/43) were malnourished or at risk for malnutrition.

**Table 1.** Characteristic of Patients in the Overall Study Population and Stratified in Survivors and Non-survivors.

Population characteristics	All (174)	Survivors (N=131)	Non-survivors (N=43)	p-value
Age, years±SD	74.26± 7.08	73.73±7.16	75.86±6.65	0.078
Gender,male (n,%)	114 (65)	86 (65.6)	28 (65.1)	0.544
BMI,kg/m2±SD	27.56±5.58	27.39±5.03	28.03±7.02	0.582
LVEF,%±SD	39.89±8.49	40.96±7.59	36.67±10.17	0.014
HR bpm,±SD	78.56±16.77	77.98±15.94	80.33±19.18	0.473
SBP, mmHg±SD	128.70±23.12	131.26±22.52	120.88±23.42	0.013
STEMI, (n,%)	92 (52.9)	69 (52.6)	23 (53.4)	0.532
Killip Class (III,IV n%)	41 (23.5)	15 (11.4)	26 (60.4)	<0.0001
Grace Score, ±SD	150.01±24.38	146.34±22.48	161.45±26.75	<0.01
MNA,±SD	22.15±4.67	22.81±4.45	20.13±4.83	<0.01
DM, (n,%)	62 (35.6)	45 (34.3)	17 (39.5)	0.354
Hypertension, (n,%)	127 (73)	99 (75.5)	28 (65.1)	0.127
Smokers, (n,%)	78 (44.8)	59 (45.0)	19(44.1)	0.352
COPD, (n,%)	38 (21.8)	27 (20.6)	11 (25.5)	0.537
Haemoglobin, mg/dl±SD	13.05±1.89	13.12±1.85	12.84±1.99	0.42
WBC x1000 /µl,±SD	10.37±3.25	10.14±3.82	11.08±3.87	0.111
Glycemia, mg/dl,±SD	135.7±53.57	133.0±43.48	143.93±66.82	0.326
GFR ml/kg/m2, ±SD	72.38±28.38	74.71±27.18	65.12±31.42	0.080
Albumine mg/dl,±SD	3.72±0.62	3.78±0.64	3.54±0.52	0.013
Troponine I ng/ml,,±SD	20.54± 23.62	14.08±12.11	40.27±36.28	<0.0001
Statins , (n,%)	168(97.1)	128 (97.7)	40 (95.2)	0.569
ASA, (n,%)	170 (97.7)	130 (98.6)	40 (95.2)	0.248
Beta-blockers, (n,%)	137 (78.7)	106 (81)	31 (72.5)	0.315
ACEi/ARBs, (n,%)	112 (64.3)	85 (64.9)	27 (61.9)	0.716

Variables are expressed as mean ±SD, binary data as percentage. P value refers to the survivors/non-survivors comparisons. ACE I indicates angiotensin-converting-enzyme inhibitor; ARBs, angiotensin receptor blockers; BMI, body mass index; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; HR, heart rate; LVEF, left ventricular ejection fraction; MNA, Mini Nutritional Assessment , SBP, systolic blood pressure; STEMI, ST-elevated myocardial infarction; WBC, white blood cells.

**3.2 Follow-up Analysis:**

Over a mean follow-up of 24.5±18.2 months, 43 deaths were registered (24.7%). Cox analysis revealed that Grace score and MNA were the only significant and independent predictors of mortality, as documented by the HR relative to 1 standard deviation (SD) variation that was 1,76 (95% CI 1,34-2,32) and 0,56 (95% CI 0,42-0,73), respectively (Table 2). The multivariate model shows a global R2 of 34,50%, suggesting that good fraction of the outcome variability is predicted. Interestingly, the contribution of the GRACE and MNA scores to the variation of the prognostic index, as documented by the partial R2, was 16.7 % and 17.8%, respectively. This latter finding indicates that the nutritional status has an impact on the survival of AMI patients that is comparable to that one exerted by the GRACE score. The graphical impact of MNA on survival is shown in Figure 1 panel A, where the survival curves relative to ± 1 SD variation of MNA mean score are reported

along with the overall Kaplan Maier curve. Survival curves relative to  $\pm 1$  SD variation of Grace mean score and the overall Kaplan Maier curve are reported in figure 1 panel B. These curves have been generated from the Cox parameters, are compared with the overall Kaplan Meier curve, and represent the survival that would be observed if the whole population would have the given MNA and Grace score.

**Table 2.** Multivariable Cox Proportional Hazard Regression Model.

Indipendent variables	HR (95% CI)	p-value	Global R2= 34.50% Fractionl R2
Age	1.02 (0.98-1.07)	0.265	NA
Gender	1.15 (0.52-2.55)	0.723	NA
BMI	1.01 (0.96-1.06)	0.536	NA
LVEF	0.96 (0.93-1.01)	0.089	NA
DM	1.50 (0.78-2.90)	0.221	NA
MNA + 1 SD	0.56 (0.42-0.73)	<0.0001	16.70%
Albumine	0.68 (0.39-3.31)	0.221	NA
Grace Score +1 SD	1.76 (1.34-2.32)	<0.0001	17.80%

HR, Hazard Ratio; CI, confidential Interval; SD, Standard Deviation; LVEF, left ventricular ejection fraction; MNA, mini nutritional assessment; DM, Diabetes Mellitus; BMI, body mass index

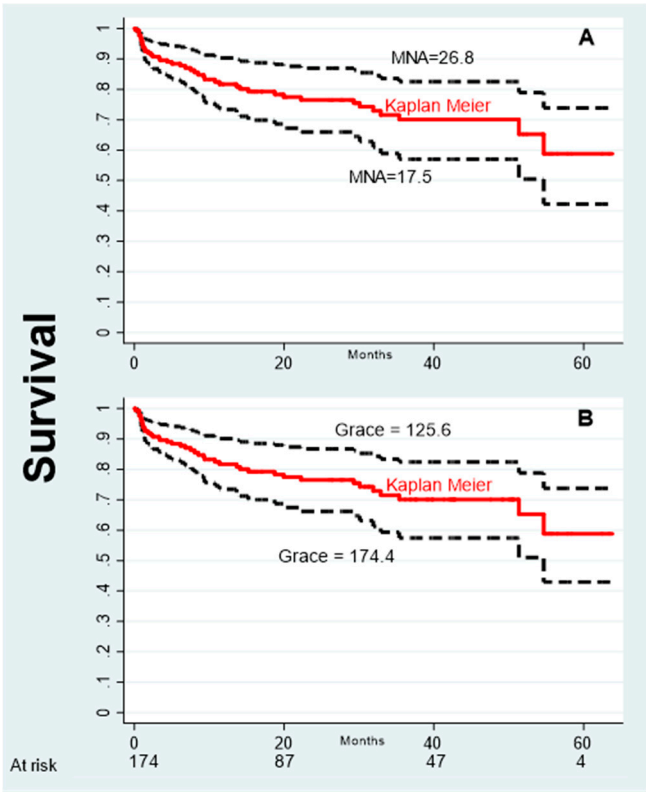
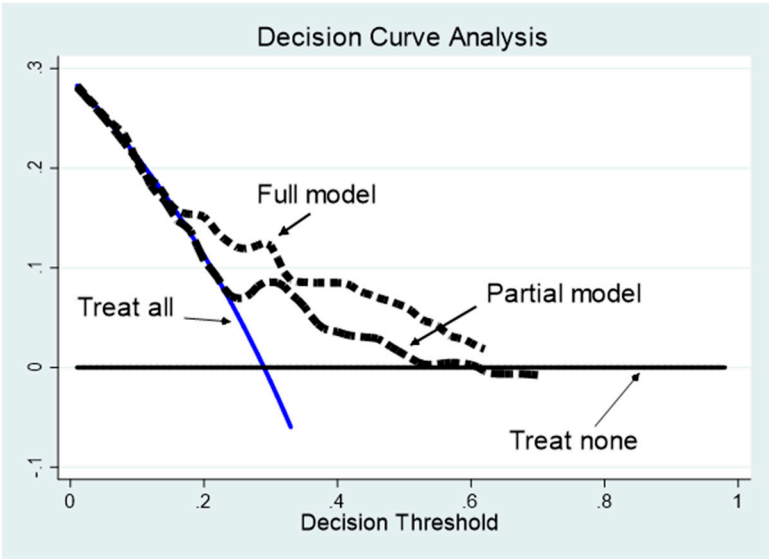




Figure 1 panel A. Survival curves (dashed black lines) at specific values of MNA (mean  $\pm$  1 SD) obtained from the Cox model adjusting for the GRACE score at the values observed in the study population (directly adjusted curves). Figure 1 panel B. Survival curves (dashed black lines) at specific values of GRACE score (mean  $\pm$  1 SD) obtained from the Cox model adjusting for the MNA score at the values observed in the study population. KM, overall Kaplan–Meier curve (continuous red line).

The clinical net benefit profiles achievable applying, in the clinical settings, the models with and without the MNA score are plotted in Figure 2. Both curves are higher than the net benefit obtained by applying the other 2 possible approaches, namely the “treat none” and “treat all” strategies. Of note, the net benefit of the full model including the MNA score draws higher than that of the partial model for a large and significant portion of the decision threshold.



**Figure 2.** Decision curve analysis. The ‘treat none’(black continuous line) and ‘treat all’(blue continuous line) curves are compared with the net benefit curves of the 2 Cox models: full model (short dash black line) and partial model without MNA (long dash black line). The full model profile is higher than the partial model profile across the critical range of the decision threshold probabilities (20–60%). Both models show curves above that of the ‘treat none’ and ‘treat all’ strategies.

**4. Discussion**

The main finding of the present study is that the nutritional status, evaluated by MNA score, is an independent predictor of long-term mortality in elderly patients with AMI. Indeed, lower MNA score was associated to higher incidence of all cause mortality. Moreover, the prognostic information obtained by MNA was comparable with that obtained by GRACE score, as well as by other established prognostic score for long- and short-term mortality in AMI patients. Finally, as demonstrated by the decision curve analysis, the introduction of MNA evaluation in the clinical setting of the acute coronary care units might have a beneficial role in identifying and management of patients with a worse prognosis.

Several authors have described MNA as an independent predictor of mortality in different settings as: free-living women [7], and after hip fracture surgery [20–21]. Although, our study population was focused on elderly with AMI, from our data results that MNA is an independent predictor of mortality. We used specific statistic models to test the impact of malnutrition on mortality and to understand its specific relationship to survival outcome. In all our models MNA demonstrated to have an important impact on predicting mortality similar to specific cardiovascular characteristics. Recently, different studies have evaluated the role of nutritional status in patients undergoing PCI [22–24], indicating that nutritional status has a predictive value on outcome. Yoo et al [13], in a similar setting described that undernutrition has an important influence on clinical

outcome of post myocardial infarction patients during hospitalization. However, in above mentioned studies, the nutritional status of elderly population has been evaluated with different scales such as prognostic nutritional index, geriatric nutritional index, and controlling nutritional status score that are generally based on albumin, lymphocytes and cholesterol levels, or body weight. Consistently, our univariate analysis indicate that albumin levels resulted as a significant predictor of mortality, although, in the multivariate analysis it lost its impact on mortality. The presence of more powerful variables, such as Grace Score, might have masked the prognostic role of albumin in our statistical model.

Grace Scoring system has been reported as one of the most robust risk stratification score in the clinical practice for patients with ACS [25]. Indeed, in our population Grace Score and its main components showed a significant predictive value. In our statistical model the MNA score, evaluated together with the Grace score, showed a predictive role, indicating a independent prognostic impact on long-term mortality.

As expected, LVEF was significantly reduced in non-survivors compared to survivors at univariate analysis. Previous studies by us others in the clinical setting of chronic HF reported LVEF as an independent predictor of long-term mortality [26-27]. However, in the present study our multivariate analysis did not reveal a significant predictive role of LVEF. At this regard, it is important to underline that we evaluated LVEF at the time of the acute coronary event and, probably, EF evaluations late after the ACS might represent a better prognostic variable for long-term mortality.

Buchloz et al [11] reported that low BMI is an independent risk factor for mortality after AMI. In our population, survivors and non-survivors were homogenous for BMI and multivariate analysis did not report any significant role.

Some studies, in patients with HF have reported an association between increased levels of inflammation biomarkers as TNF- $\alpha$ , malnutrition status and poor outcome [28-30]. Mechanistically, the activation of neuro-hormonal and inflammatory pathways, that characterize cardiovascular disease, may increase the catabolic demand and patients with already a poor nutritional status may be more vulnerable to cardiac events. Moreover, the protective and beneficial role of physical activity on ischemic cardiac disease is well recognized [30], as well as the link between malnutrition and physical decondition is also well documented [31]. Thus, it is plausible to assume that poor nutritional status by limiting the physical performance of post-ischemic elderly patients may influence their outcome. However, highlighting the mechanisms by which malnutrition affects mortality in ACS patients is beyond the purposes of the present study.

It is well known that nutritional support can correct the nutritional deficit and, as reported from several studies, the use of supplemental strategies reduces the in-hospital mortality [33]. The results of our study strongly suggest that beside overall cardiovascular intervention strategies, elderly patients may benefit from geriatric evaluations including investigation of the nutritional status.

*Study Limitation:*

This study is a single center experience in a relative small number of patients; thus, our findings deserve confirmation in larger multi-centric studies. Moreover, we did not evaluate if a therapeutic intervention aiming to correct the nutritional status would affect mortality in our study population. Future studies are needed to clarify weather correction of the nutritional status would improve prognosis in elderly patients with AMI.

**5. Conclusions**

Nutritional status is an independent predictor of long-term mortality among elderly patients with AMI. Measurement of MNA score in elderly patients with AMI may help prognostic stratification and identification of patients with/at risk of malnutrition in order to apply interventions to improve nutritional status.

**Author Contributions:** Conceptualization, klara komici, Carmine Morisco, Dario Leosco, Nicola Ferrara and Giuseppe Rengo; Data curation, klara komici, Angela Mancini, Leonardo Bencivenga, Maddalena Conte, Sandra Provenzano, Fabrizio Vincenzo, Lucia Visaggi and Ilaria Ronga; Formal analysis, klara komici and Dino Franco

Vitale; Methodology, Dino Franco Vitale and Angela Mancini; Resources, Bruno Trimarco; Supervision, Grazia Maria Corbi and Giuseppe Rengo; Writing – original draft, klara komici, Grazia Maria Corbi and Giuseppe Rengo.

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