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Original article

Lipid paradox in patients with acute myocardial infarction: Potential impact of malnutrition

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SUMMARY

Background & aims: Aggressive lipid reduction is recommended for patients with AMI, but reverse epidemiology, the lipid paradox, has been reported in several clinical studies. The cause of lipid paradox remains uncertain, and nutrition is one possible explanation. In this single-center retrospective study, we investigated the relationships between baseline LDL concentrations and clinical outcomes in patients with AMI, stratified by different nutritional status.

Methods: Totally 409 patients were enrolled for analysis. The Nutritional Risk Index (NRI) was used to estimate the risk of malnutrition. Subjects were grouped into tertiles according to their NRIs. Clinical outcomes were compared among patients with varying NRIs and LDL levels.

Results: Patients in the lowest NRI tertile had increased incidences of in-hospital mortality, cardiogenic shock, decompensated heart failure, renal failure, and sepsis. This tertile was also associated with increased long-term mortality during the follow-up period of 832 ± 744 days. Mortality was increased among patients with baseline LDL concentrations ≤ 70 mg/dL in the lowest NRI tertile (log rank test, $p = 0.0257$), but not in the high or median tertiles. Moreover, baseline LDL level ≤ 70 mg/dL was an independent risk factor of all-cause mortality (adjusted hazard ratio = 1.73; 95% confidence interval, 1.01–2.94; $p = 0.045$) in the lowest NRI tertile.

Conclusions: Lipid paradox was observed in the high-risk of malnutrition population among patients with AMI. Aggressive lipid-lowering therapy is still recommended for patients with AMI and fair nutritional status. However, when treating patients at high risk of malnutrition, the improvement of nutritional status may be more beneficial than strict LDL control.

Abbreviations: ACS, acute coronary syndrome; AMI, acute myocardial infarction; BMI, body mass index; CAD, coronary artery disease; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; LV, left ventricle; NRI, nutritional risk index; Non-STEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; TG, triglyceride; WBC, white blood cell.

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1. Introduction

With the increasing prevalence of obesity and hyperlipidemia, the incidence of coronary artery disease (CAD) is rising worldwide, which is believed to be the result of stationary lifestyles and fat-rich diets in modern life [1–3]. Dietary modifications, such as the reduction of saturated fat intake, limitation of alcohol consumption, and increased consumption of healthier plant-based foods, have been suggested for primary and secondary prevention of CAD [4,5]. To attenuate the progression of atherosclerosis and vascular inflammation, aggressive lipid-lowering therapy (dietary adjustment or medication) has been recommended for patients with acute coronary syndrome (ACS) [6,7]. However, several large cohort studies have shown that lower low-density lipoprotein (LDL) levels are associated with an increased risk of in-hospital mortality following acute myocardial infarction (AMI), referred to as the lipid paradox [8–10]. Possible explanations of the lipid paradox include liver dysfunction after AMI [11] and the reflection of coronary disease severity [12]. Few studies have linked this paradox to the presence of malnutrition.

In this single-center observational study, we investigated relationships between baseline serum LDL levels and clinical outcomes in patients with AMI, stratified by nutritional status. Among various nutrition screening tools used to assess clinical outcomes in hospitalized patients [13,14], the Nutritional Risk Index (NRI) has been applied to patients with decompensated heart failure and those undergoing surgery [15–17]. We used the NRI to evaluate the risk of malnutrition and prognosis in patients with AMI, and to clarify the associations among nutritional status, LDL concentration, and adverse cardiovascular events.

2. Materials and methods

2.1. Study population

In this retrospective study, we screened 604 patients admitted to the cardiac intensive care unit (ICU) at Taipei Veterans General Hospital due to AMI [ST-segment elevation myocardial infarction (STEMI) or non-STEMI] between January 2012 and June 2014. AMI was defined as >0.1 ng/mL elevation of the serum troponin I level, combined with clinical presentations of typical chest pain and/or electrocardiographic ST-segment changes [18]. Patients without available data on the serum albumin level (n = 174) or lipid profile (n = 10), especially the LDL concentration, were excluded from the analysis. Patients aged <40 years (n = 11) were also excluded. After the exclusion of 195 patients, 409 patients were enrolled for analysis. This study was conducted according to the principles of the Declaration of Helsinki and was approved by the Research Ethics Committee of Taipei Veterans General Hospital. All participants provided written informed consent.

2.2. Measurement of clinical and nutritional variables

After enrollment, the medical record of each patient was reviewed in detail. Patients' clinical characteristics, including age, sex, body weight, body mass index (BMI), comorbidities [hypertension, diabetes mellitus, heart failure (HF), previous stroke], type of AMI, Killip classification, and left ventricular (LV) systolic function, were collected retrospectively. LV systolic function, blood chemistry data, blood pressure, and heart rate were recorded on the day of ICU admission. LV systolic function was evaluated by bedside echocardiography. The blood cell count and blood chemical parameters were measured using routine laboratory methods. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease formula [19].

Serum albumin was measured on the first day of ICU admission. Lipid profiles, including total cholesterol, triglyceride (TG), high-density lipoprotein, and LDL concentrations, were obtained after at least 8 h of fasting. The NRI was calculated as 1.519 × albumin (g/L) + 41.7 × (present body weight/ideal body weight) [20,21]. Ideal body weight was estimated by the Lorentz formula: [height (cm) − 100 − (height − 150)/4] for men and [height − 100 − (height − 150)/2] for women [22]. Patients were grouped into tertiles according to their NRIs. The lowest tertile of NRI level (NRI < 84.9) was defined as high risk of malnutrition, middle tertile of NRI level (NRI = 84.9–99.6) as moderate risk of malnutrition and highest tertile of NRI level (NRI > 99.6) as low risk of malnutrition.

To investigate the prognostic impact of the LDL concentrations in patients with different risks of malnutrition, we stratified the study cohort by serum LDL level. The prognoses of study subjects who had achieved the target LDL concentration (≦70 mg/dL for a population at very high risk of atherosclerotic cardiovascular disease) [23,24] before AMI were compared with those of subjects with higher baseline serum LDL levels. To determine whether lipid paradox is associated with malnutrition or hypoalbuminemia, we also evaluated the prognostic impact of LDL concentrations in patients stratified by different albumin levels and BMI, another well-adapted nutritional index [25]. A flowchart of patient enrollment and classification is shown in Fig. 1.

2.3. Study endpoints and patient follow-up

Short-term and long-term adverse events occurring in the study sample were recorded. Short-term adverse events included death, cardiogenic shock, decompensated HF, respiratory failure, renal failure, and sepsis during hospitalization. Cardiogenic shock was defined as persistent hypotension (systolic blood pressure <80 mmHg or ≥30 mmHg reduction in mean blood pressure compared with baseline) with evidence of elevated LV filling pressure or decreased LV systolic function on echocardiography [26]. Decompensated HF was defined as rapid exacerbation of HF with typical symptoms and signs [27]. Respiratory failure was defined as the need for endotracheal tube intubation and mechanical support [28]. Renal failure was defined as acute deterioration of renal function that required renal replacement therapy [29]. Sepsis was defined as the presence of two or more systemic inflammatory response syndrome criteria and clinical evidence of infection [30]. All enrolled patients were followed in our outpatient department at 2 weeks after discharge and then every 3 months for medication refills. The patients were followed until November 2017 or the occurrence of long-term adverse cardiovascular events, including all-cause mortality, cardiovascular mortality, nonfatal stroke, nonfatal MI, and target vessel revascularization. The adverse cardiovascular events are defined in detail in our previous study [31].

2.4. Statistical analysis

Continuous variables were compared between groups using analysis of variance or the Kruskal–Wallis test. Categorical variables were compared using the chi-squared test. Continuous variables were expressed as means ± standard deviations, and categorical variables were expressed as numbers (percentages). Kaplan–Meier survival curves and the log-rank test were used to compare the survival rates of patients with different NRIs, albumin levels, and BMI. Survival was also compared between patients with different LDL concentrations in NRI subgroups. Cox proportional-hazard regression analysis was performed to investigate predictors of long-term mortality. Variables with p values < 0.1 in the

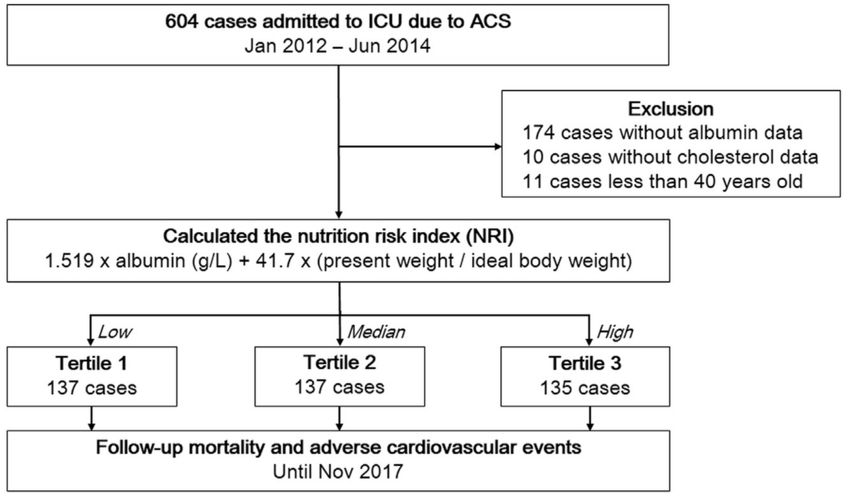

Fig. 1. Flowchart of Patient Enrollment. ICU, intensive care unit; ACS, acute coronary syndrome.

univariable regression analysis were entered into the multivariable regression analysis. Multivariable Cox regression analysis was performed for the whole study cohort and for subgroups with different malnutrition risks. P values < 0.05 were considered to be statistically significant. All analyses were performed using SPSS statistical software (version 23.0; IBM Corporation, Armonk, NY, USA).

3. Results

3.1. Baseline characteristics

In total, 409 patients with AMI (76% male; mean age, 75.2 ± 13.2 years) were included in the analysis. The baseline characteristics of the study subjects are shown in Table 1. Patients in the lowest NRI tertile were significantly older and had lower diastolic blood pressures, higher heart rates, and a higher incidence of Killip class III–IV AMI; a smaller percentage of these patients underwent percutaneous coronary intervention (PCI) after AMI. The hemoglobin level and baseline eGFR differed significantly among NRI tertiles. Nutritional parameters, including BMI and albumin, total cholesterol, TG, and LDL levels, were significantly decreased in patients with lower NRIs. The lowest NRI group included more patients with baseline LDL levels ≤70 mg/dL. Statin usage before and after the occurrence of AMI did not differ among the three groups.

3.2. Outcomes stratified by nutritional status and LDL concentration

Short-term and long-term outcomes are summarized in Table 2. A total of 60 (14.7%) patients died during hospitalization for AMI. Patients with NRIs <89.4 had the highest incidences of in-hospital mortality (19.7%), cardiogenic shock (31.6%), decompensated HF (40.9%), respiratory failure (41.6%), renal failure (21.2%), and sepsis (26.3%). During the follow-up period (mean duration, 832 ± 744 days), the lowest NRI tertile was associated significantly with a greater occurrence of all-cause mortality (41.6%) and higher cardiovascular mortality rate (29.2%), but not with the greater occurrence of nonfatal MI, stroke, or target vessel revascularization.

The survival rates of patients, stratified by NRI and LDL level, are shown in Fig. 2. The overall death-free survival rate was significantly higher in patients with higher NRIs (log rank test, $p < 0.0001$; Fig. 2A). The mortality rate did not differ significantly between patients at low risk of malnutrition with baseline LDL concentrations >70 mg/dL and ≤70 mg/dL (log rank test, $p = 0.4486$; Fig. 2B). In the moderate risk malnutrition group, the mortality rate was lower among patients with baseline LDL levels ≤70 mg/dL than among those with LDL levels >70 mg/dL, but this difference was not significant (log rank test, $p = 0.0660$; Fig. 2C). Among patients at high risk of malnutrition, subjects with baseline serum LDL levels ≤70 mg/dL had significantly higher mortality rates than did those with higher baseline LDL levels (log rank test, $p = 0.0257$; Fig. 2D). The survivals of patients stratified by different albumin and BMI levels were summarized in Supplement Fig. 1. Patients with lower albumin concentrations were significantly associated with higher incidence of mortality (log rank $p < 0.0001$). However, among patients with serum albumin <3.0 mg/dL, the lowest albumin tertile, mortality rates were similar between subjects with different baseline LDL concentrations (log rank $p = 0.6702$). In contrast, subjects with baseline LDL levels ≤70 mg/dL trended to have higher mortality rates than those with higher LDL levels in the subgroup of BMI ≤22.5, the lowest tertile of BMI (log rank $p = 0.0566$).

3.3. Prognostic factors for subjects with different risks of malnutrition

In the univariable Cox regression analysis, old age, female sex, lower blood pressure and higher heart rate at admission, underlying hypertension and heart failure, Killip class III–IV AMI, non-receipt of PCI revascularization, higher serum white blood cell (WBC) count and troponin-I levels, and lower hemoglobin level, eGFR, LV ejection fraction, and nutritional values (NRI tertile, BMI, albumin and TG levels) were associated significantly with the increased incidence of all-cause mortality after AMI. In the multivariable Cox regression analysis, old age, HF, non-receipt of PCI, higher WBC count and troponin-I level, and lower albumin level remained significantly associated with all-cause mortality (Table 3). Age [Hazard ratio (HR) = 1.04; 95% confidence interval (CI), 1.01–1.06; $p = 0.002$], underlying HF (HR = 1.83; 95% CI, 1.08–3.10; $p = 0.026$), PCI revascularization (HR = 0.55; 95% CI, 0.32–0.96; $p = 0.036$), WBC count (HR = 1.00; 95% CI, 1.00–1.00; $p = 0.039$), troponin-I (HR = 1.01; 95% CI, 1.00–1.01; $p = 0.011$), and albumin levels (HR = 0.54; 95% CI, 0.31–0.94; $p = 0.031$) were independent predictors of all-cause mortality for patients with AMI.

Table 1
Baseline characteristics of patients, stratified by nutritional status.

Variables		Total	NRI <89.4	NRI: 89.4–99.6	NRI >99.6	*P* value
		n = 409	n = 137	n = 137	n = 135	
Age		75.21 ± 13.23	80.15 ± 10.63	77.66 ± 11.05	67.71 ± 14.36	<0.001
Men		309 (75.6%)	103 (75.2%)	99 (72.3%)	107 (79.3%)	0.403
SBP		136.15 ± 29.55	134.70 ± 31.44	135.66 ± 29.87	138.31 ± 27.25	0.475
DBP		75.78 ± 17.53	71.90 ± 18.49	76.82 ± 17.31	78.66 ± 16.13	0.001
Heart rate		86.77 ± 19.93	90.60 ± 21.02	85.45 ± 19.89	84.23 ± 18.32	0.019
Hypertension		306 (74.8%)	106 (77.4%)	104 (75.9%)	96 (71.1%)	0.462
Diabetes		191 (46.7%)	59 (43.1%)	70 (51.1%)	62 (45.9%)	0.402
Heart failure		68 (16.6%)	26 (19.0%)	26 (19.0%)	16 (11.9%)	0.191
Previous stroke		46 (11.2%)	22 (16.1%)	14 (10.2%)	10 (7.4%)	0.070
Types of MI	STEMI	121 (29.6%)	37 (27.0%)	39 (28.5%)	45 (33.3%)	0.491
	NSTEMI	288 (70.4%)	100 (73.0%)	98 (71.5%)	90 (66.7%)	
Killip	class I–II	254 (62.1%)	69 (50.4%)	89 (65.0%)	96 (71.1%)	0.001
	class III–IV	155 (37.9%)	68 (49.6%)	48 (35.0%)	39 (28.9%)	
Underwent PCI		320 (78.2%)	96 (70.1%)	107 (78.1%)	117 (86.7%)	0.004
Laboratory data						
WBC (x 10^3)		10.99 ± 4.73	11.45 ± 5.30	10.24 ± 4.35	11.29 ± 4.45	0.056
Hb		11.99 ± 2.56	11.00 ± 2.02	11.70 ± 2.42	13.30 ± 2.66	<0.001
eGFR		47.01 ± 27.17	41.42 ± 26.68	45.08 ± 25.22	54.59 ± 28.01	<0.001
Glucose		174.50 ± 112.85	179.80 ± 142.71	171.13 ± 78.66	172.83 ± 110.19	0.522
Troponin-I		10.51 ± 30.83	12.65 ± 25.74	10.88 ± 43.47	7.95 ± 16.92	0.454
LVEF (%)		44.37 ± 12.67	44.20 ± 13.50	42.51 ± 13.10	46.29 ± 11.26	0.129
Nutritional variables						
BMI		24.25 ± 4.04	21.25 ± 2.73	24.07 ± 2.80	27.47 ± 3.79	<0.001
Albumin		3.22 ± 0.53	2.75 ± 0.41	3.26 ± 0.36	3.66 ± 0.38	<0.001
Total Cholesterol		152.52 ± 44.24	144.20 ± 50.27	150.25 ± 36.77	162.88 ± 43.01	0.001
TG		117.51 ± 78.05	97.39 ± 55.91	111.80 ± 66.39	142.04 ± 97.86	<0.001
HDL		37.78 ± 12.99	37.64 ± 15.77	39.17 ± 11.67	36.47 ± 10.86	0.236
LDL		94.62 ± 40.95	86.91 ± 41.86	93.25 ± 40.87	103.26 ± 38.77	<0.001
LDL ≤70		112 (27.4%)	50 (36.5%)	40 (29.2%)	22 (16.30)	0.001
Statin usage before MI		69 (16.9%)	18 (13.4%)	29 (21.8%)	22 (16.30)	0.189
Statin usage after MI		300 (73.3%)	92 (67.7%)	105 (76.6%)	103 (76.3)	0.164

SBP, systolic blood pressure; DBP, diastolic blood pressure; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non–ST-segment elevation myocardial infarction; WBC, white blood cell; Hb, hemoglobin; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; BMI, body mass index; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MI, myocardial infarction.

Table 2
Outcomes according to nutritional status.

Outcomes	NRI <89.4	NRI: 89.4–99.6	NRI >99.6	*P* value
	n = 137	n = 137	n = 135	
Short-term outcomes				
In-hospital mortality	27 (19.7%)	24 (17.5%)	9 (6.7%)	0.005
Cardiogenic shock	43 (31.6%)	35 (25.5%)	25 (18.5%)	0.046
Decompensated HF	56 (40.9%)	52 (38.0%)	29 (21.5%)	0.001
Respiratory failure	57 (41.6%)	34 (24.8%)	25 (18.5%)	<0.001
Renal failure underwent RRT	29 (21.2%)	13 (9.5%)	10 (7.4%)	0.001
Sepsis	36 (26.3%)	14 (10.2%)	13 (9.6%)	<0.001
Long-term outcomes				
All-cause mortality	57 (41.6%)	46 (33.6%)	20 (14.8%)	<0.001
Cardiovascular mortality	40 (29.2%)	30 (21.9%)	15 (11.1%)	0.001
Nonfatal stroke	4 (2.9%)	7 (5.1%)	1 (0.7%)	0.105
Nonfatal MI	14 (10.2%)	23 (16.8%)	17 (12.6%)	0.268
Target-vessel revascularization	23 (17.3%)	21 (15.6%)	20 (15.0%)	0.871

NRI, Nutritional Risk Index; HF, heart failure; RRT, renal replacement therapy; MI, myocardial infarction.

In the subgroup analysis, the eGFR, troponin-I level, and TG level were associated independently with all-cause mortality in patients at moderate risk of malnutrition (Supplement Table 1). Similar to the results obtained for the whole study cohort, old age, lower systolic blood pressure, and eGFR were independent predictors of all-cause mortality in subjects at low risk of malnutrition (Supplement Table 2). However, the predictive factors differed markedly in patients at high risk of malnutrition. In the univariable Cox regression analysis, only the WBC count, BMI, albumin level, and baseline LDL concentration ≤70 mg/dL were associated significantly with all-cause mortality in patients in the lowest NRI tertile. In these patients at high risk of malnutrition, an increased WBC count (HR = 1.00; 95% CI, 1.00–1.00; $p = 0.013$), lower BMI (HR = 0.88; 95% CI, 0.80–0.96; $p = 0.004$), lower serum albumin level (HR = 0.48; 95% CI, 0.26–0.89; $p = 0.020$), and baseline LDL level ≤70 mg/dL (HR = 1.73; 95% CI, 1.01–2.94; $p = 0.045$) were independent risk factors of all-cause mortality in the multivariable Cox regression analysis (Table 4). Statin use before or after AMI was not associated with all-cause mortality in the high-risk malnutrition group.

4. Discussion

In this retrospective study of 409 cases of AMI, patients in the lowest NRI tertile (the high-risk malnutrition population) had

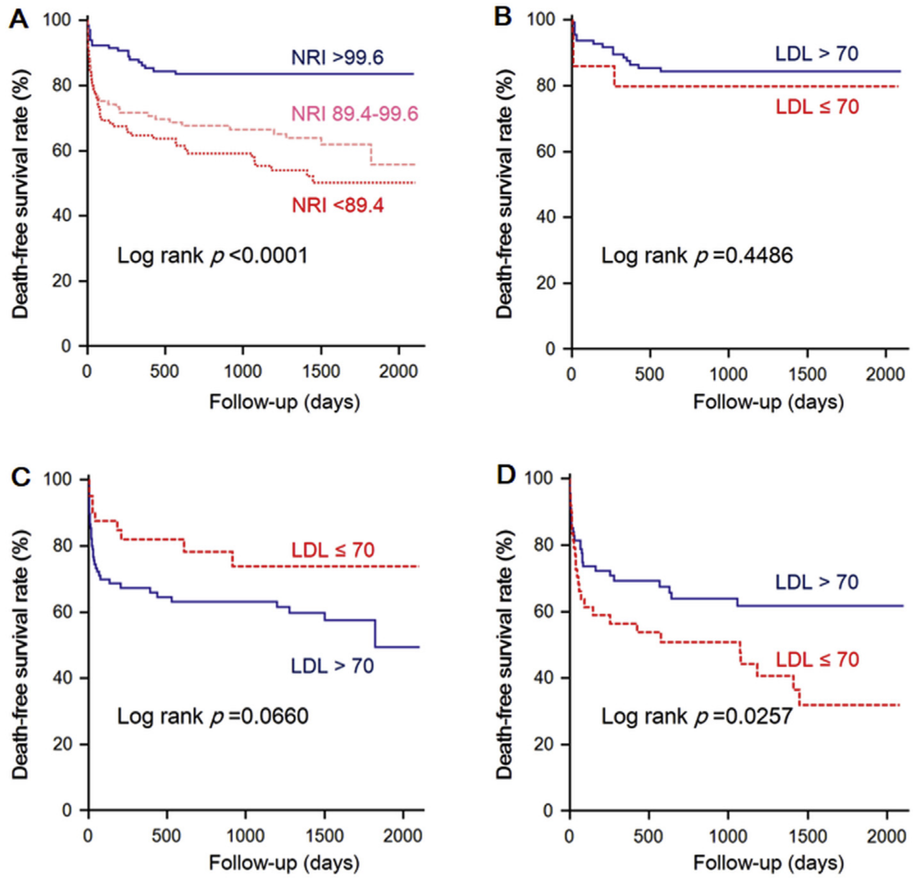

Fig. 2. Kaplan–Meier curves of death-free overall survival stratified by nutritional status **(A)** and by low-density lipoprotein level in patients with low **(B)**, moderate **(C)**, and high **(D)** risks of malnutrition. NRI, Nutritional Risk Index; LDL, low-density lipoprotein.

increased incidences of in-hospital mortality, cardiogenic shock, decompensated HF, respiratory failure, renal failure, and sepsis. Patients with the lowest NRIs also showed increased long-term mortality during the follow-up period. Of note, the lipid paradox was observed only in the high-risk malnutrition population of patients with AMI. Baseline LDL level ≤70 mg/dL was associated with increased incidence of all-cause mortality in the high-risk malnutrition population, but not in the low or moderate-risk groups. In addition, baseline LDL level ≤70 mg/dL was an independent risk factor of all-cause mortality in the high-risk malnutrition population.

AMI is the leading cause of death worldwide, and it poses a substantial economic burden on healthcare systems. Like hypertension and diabetes, hyperlipidemia is a well-known risk factor as well as the treatment goal for AMI [32]. LDL plays principal roles in atherosclerosis and vascular inflammation. In an *in vitro* study, LDL promoted Toll-like receptor inflammatory signaling via interaction with macrophages [33,34]. In clinical trials, significantly less death from cardiovascular disease and occurrence of major coronary events and nonfatal stroke were found in patients receiving combination therapy with simvastatin and ezetimibe to reduce the LDL level to 53.7 mg/dL after AMI [35]. Primary prevention of cardiovascular disease with statin therapy according to calculated risk scores is recommended in the National Institute for Health and Care Excellence guidelines [36], ACC/AHA 2013 guidelines [37], and 2016 ESC/EAS guidelines [7]. After ACS, statin therapy for secondary prevention of cardiovascular disease with the therapeutic target of LDL level <70 mg/dL has been recommended [24,37,38]. The above evidences tended to achieve lower serum LDL levels for patients with AMI.

Cautiously control of LDL levels before and after ACS has been well studied. “The lower, the better” is a well-known slogan for lipid-lowering therapy in patients with CAD. However, the lipid paradox has been reported in several clinical studies. In one study enrolling 9751 patients with AMI undergoing PCI, patients were divided into five groups according to LDL-C level (<70, 70–99, 100–129, 130–159, and ≥160 mg/dL). In-hospital clinical outcomes, including the occurrence of complications and death, were better with increasing LDL concentration, except in patients with LDL cholesterol levels ≥160 mg/dL [39]. The “lipid paradox” is also observed in patients with chronic HF [40,41]. Though the cause of lipid paradox remains uncertain, following possible explanations have been offered. First, a lower baseline LDL level may be an indicator of high-risk population following AMI. These patients may have extensive vascular inflammation, leading to the occurrence of AMI even in the context of lower LDL concentrations. Moreover, these subjects may not receive aggressive statin therapy because of their lower baseline LDL levels. Second, lower LDL levels may be associated with poor nutritional status, making patients more vulnerable to the acute stress after AMI. A similar phenomenon is the obesity paradox, which refers to the reverse epidemiology observed in patients with end-stage renal disease, chronic obstructive pulmonary disease, and AMI [42–44]. Significantly fewer major adverse cardiovascular events were observed in patients with STEMI and BMIs of 30.0–34.9 kg/m^2 compared with patients with normal BMIs [45]. Third, serum lipoprotein might be a buffering factor involved in the modification of systemic inflammation in malnourished patients. Higher serum lipoprotein levels were found to have an anti-inflammatory effect

Table 3
Multivariable cox regression results for all-cause mortality in patients with acute myocardial infarction (whole study cohort, $n = 409$).

Variables	Univariable analysis		Multivariable analysis[a]	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age	1.03 (1.02–1.05)	<0.001	1.04 (1.01–1.06)	0.002
Female gender	1.47 (1.00–2.17)	0.052		
SBP	0.99 (0.98–1.00)	<0.001		
DBP	0.98 (0.97–0.99)	0.001		
Heart rate	1.01 (1.00–1.02)	0.020		
Hypertension	1.90 (1.12–3.07)	0.009		
Diabetes	1.13 (0.80–1.62)	0.489		
Heart failure	2.00 (1.34–3.00)	0.001	1.83 (1.08–3.10)	0.026
Previous stroke	1.26 (0.73–2.16)	0.406		
STEMI	0.92 (0.62–1.37)	0.686		
Kallips class III–IV	2.38 (1.67–3.40)	<0.001		
Underwent PCI	0.40 (0.27–0.58)	<0.001	0.55 (0.32–0.96)	0.036
WBC	1.00 (1.00–1.00)	0.001	1.00 (1.00–1.00)	0.039
Hb	0.85 (0.79–0.90)	<0.001		
eGFR	0.98 (0.97–0.99)	<0.001		
Glucose	1.00 (1.00–1.00)	0.383		
Troponin-I	1.01 (1.00–1.01)	0.001	1.01 (1.00–1.01)	0.011
LVEF (%)	0.98 (0.96–0.99)	0.008		
Nutritional variables				
NRI >99.6	*Ref*	*Ref*		
NRI 84.9–99.6	2.69 (1.59–4.54)	<0.001		
NRI <84.9	3.47 (2.08–5.79)	<0.001		
BMI	0.93 (0.88–0.97)	0.002		
Albumin	0.37 (0.26–0.51)	<0.001	0.54 (0.31–0.94)	0.031
Total cholesterol	1.00 (0.99–1.00)	0.502		
TG	1.00 (0.99–1.00)	0.035		
HDL	1.00 (0.98–1.02)	0.971		
LDL ≤70	1.38 (0.95–2.02)	0.094		
Statin before AMI	0.84 (0.52–1.38)	0.494		
Statin after AMI	0.91 (0.61–1.35)	0.641		

SBP, systolic blood pressure; DBP, diastolic blood pressure; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non–ST-segment elevation myocardial infarction; WBC, white blood cell; Hb, hemoglobin; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; BMI, body mass index; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PCI, percutaneous coronary intervention; NRI, Nutritional Risk Index.
[a] The model includes variables with p values < 0.1 in univariable analysis.

Table 4
Multivariable cox regression results for all-cause mortality in patients with acute myocardial infarction at high risk of malnutrition (NRI < 89.4, $n = 137$).

Variables	Univariable analysis		Multivariable analysis[a]	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age	1.00 (0.98–1.03)	0.745		
Female gender	1.13 (0.62–2.07)	0.690		
SBP	0.99 (0.99–1.00)	0.159		
DBP	1.00 (0.99–1.02)	0.809		
Heart rate	1.01 (1.00–1.02)	0.257		
Hypertension	1.28 (0.66–2.48)	0.464		
Diabetes	0.96 (0.57–1.64)	0.893		
Heart failure	1.60 (0.87–2.93)	0.132		
Previous stroke	0.84 (0.38–1.87)	0.671		
STEMI	1.40 (0.79–2.47)	0.253		
Kallips class III–IV	1.62 (0.95–2.75)	0.076		
Underwent PCI	0.67 (0.38–1.16)	0.152		
WBC	1.00 (1.00–1.00)	0.005	1.00 (1.00–1.00)	0.013
Hb	1.00 (0.87–1.14)	0.969		
eGFR	0.99 (0.98–1.00)	0.084		
Glucose	1.00 (1.00–1.00)	0.450		
Troponin-I	1.01 (1.00–1.01)	0.264		
LVEF (%)	0.98 (0.96–1.01)	0.217		
Nutritional variables				
BMI	0.90 (0.81–0.99)	0.025	0.88 (0.80–0.96)	0.004
Albumin	0.51 (0.27–0.97)	0.040	0.48 (0.26–0.89)	0.020
Total cholesterol	1.00 (1.00–1.01)	0.359		
TG	1.00 (1.00–1.01)	0.315		
HDL	0.99 (0.97–1.01)	0.444		
LDL ≤70	1.80 (1.07–3.04)	0.028	1.73 (1.01–2.94)	0.045
Statin before AMI	1.22 (0.60–2.49)	0.587		
Statin after AMI	0.87 (0.50–1.52)	0.624		

SBP, systolic blood pressure; DBP, diastolic blood pressure; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non–ST-segment elevation myocardial infarction; WBC, white blood cell; Hb, hemoglobin; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; BMI, body mass index; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PCI, percutaneous coronary intervention; NRI, Nutritional Risk Index.
[a] The model includes variables with p values < 0.1 in univariable analysis.

via the inactivation of lipopolysaccharide signaling in patients with chronic HF [46,47].

Hyperlipidemia and obesity are well-known risk factors for CAD, and guidelines recommend weight reduction and dietary modification to ameliorate insulin resistance and hyperlipidemia [48]. However, the lipid and obesity paradoxes did present in some observational studies. Previous study reporting the lipid paradox focused on the general population of ACS, suggesting lipid paradox may be the result of confounding factors, such as statin treatment or intensive medical contact [9]. In addition, the previous study revealed no difference in 1-year mortality among patients with different LDL levels after adjustment for possible risk factors, including past history, BMI, blood chemistry parameters, and medication history [39].

In the critical care setting, a change in a single serum protein marker (albumin, prealbumin, transferrin, or retinol-binding protein) may reflect an acute-phase response and may not accurately represent the patient's nutritional status [49]. In the present study, we thus evaluated patients' nutritional status using the NRI, which has been validated to be associated with the length of hospitalization and risk of complications, and to predict outcomes in hospitalized patients [13,50]. Our results clearly show that the lipid paradox was presented only in malnutrition patients, either patients at the lowest NRI or BMI tertile. Though albumin was also a predictor of mortality in our study, lipid paradox was not observed in subjects with hypoalbuminemia. Moreover, during the long-term follow-up period, a lower baseline LDL level was an independent risk factor of increased mortality among patients at high risk of malnutrition. Further prospective studies are warranted to explore the roles of the serum LDL level and nutritional status in different stages of AMI.

The study has several limitations. First, it was a single-center, retrospective study. The older age of our patients might not represent the general age distribution, which limits the generalization of our results. In addition, confounding factors such as vascular inflammation and muscle mass could not be assessed fully due to the observational nature of this study. Finally, the use of the NRI to evaluate nutritional status led to the exclusion of 174 patients without albumin data, potentially resulting in underestimation of the average albumin level and NRI in our cohort.

In conclusion, the presence of the lipid paradox varied with nutritional status. Baseline LDL levels ≤70 mg/dL were associated with a higher mortality rate in patients with AMI at high risk of malnutrition, but not in those at low or moderate risk. Weight reduction and lipid-lowering therapy are still recommended for patients with AMI and fair nutritional status. However, when treating patients at high risk of malnutrition, the improvement of nutritional status may be more beneficial than strict LDL control.

Statement of authorship

Research idea and study design: Lu YW, Chou RH, and Wu PS; data acquisition: Lu YW, Lu SF, Ku YC, Chang CC, and Tsai YL; data analysis/interpretation: Lu YW, Chou RH, and Huang PH; statistical analysis: Lu YW, Lu SF, and Chou RH; supervision or mentorship: Kuo CS, Wu CH, and Huang PH. Each author contributed important intellectual content during manuscript drafting or revision. All authors read and approved the final manuscript.

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Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2018.10.008.

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