Clinical research

The "cholesterol paradox" among inpatients – retrospective analysis of medical documentation

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Abstract

Introduction: There is evidence of positive relationships between cholesterol concentration and risk of cardiovascular diseases. However, higher mortality in patients with a low cholesterol level has been reported (the "cholesterol paradox").

Material and methods: Medical records of 34 191 inpatients between 2014 and 2016 were reviewed and the relationships between total (TC), low-density lipoprotein (LDL-C) and high-density lipoprotein (HDL-C) cholesterol and triglyceride blood concentrations and all-cause in-hospital death and readmission within 14 and 30 days and 1 year were determined in univariate and multivariate analyses.

Results: Patients with TC in the lower quartile and LDL-C < 70 mg/dl had greater risk of the outcomes measured than individuals with a TC level in the remaining quartiles and LDL-C ≥ 70 mg/dl. Moreover, patients with TC in the highest quartile, OR (95% CI): 0.36 (0.13–0.99), $p < 0.05$, and LDL-C ≥ 115 mg/dl, OR (95% CI): 0.53 (0.37–0.77), $p < 0.05$, had the lowest all-cause in-hospital mortality. However, multivariate analysis using logistic regression and a Cox proportional hazard model showed no significant influence of blood lipid levels on the occurrence of the outcomes measured.

Conclusions: A significant effect of a "cholesterol paradox" linking better prognosis with higher blood lipid concentration was found only in univariate analysis but, after adjustment for clinical characteristics in multivariate analysis, the plasma lipid level had a neutral influence on the occurrence of the measured outcomes. This suggests that a low cholesterol level should be interpreted as a biomarker of illness severity.

Key words: lipids, cholesterol paradox, in-hospital mortality, readmission risk.

Introduction

Blood plasma lipid concentration is affected by several factors, including genetic, lifestyle and environment, and those related to pharmacotherapy. The determination of lipids is used in everyday clinical practice as a biomarker for cardiovascular risk stratification in primary cardiovascular event (CVE) prevention, as a biomarker for hypolipidemic treatment both in primary and secondary CVE prevention in short-and long-term follow-up, as a parameter of metabolic syndrome and nephrotic syndrome diagnosis, as well as a risk factor for acute pancreatitis and liver steatosis [1–3]. Moreover, blood total cholesterol (TC) is used as a marker of malnutrition, both alone and as a parameter of the Controlling Nutritional Status (CONUT) score [4, 5], and triglycerides are useful in the safety monitoring of enteral and parenteral nutrition.

Dyslipidemia is recognized as one of the strongest risk factors for atherosclerosis and CVE [1–3]. During a very long-term, up to a maximum of 46 years, follow-up of 3277 midlife healthy men in the Helsinki Businessmen Study, a baseline total cholesterol blood concentration below 154 mg/dl was related to the lowest mortality and a higher score in the RAND-36 physical functioning scale in old age [6]. It has also been well evidenced that hypolipemic therapy, mainly with statins and recently with inhibitors of proprotein convertase subtilisin/kexin type 9 (PCSK9), decreases overall and cardiovascular mortality, reduces risk of CVE and has established a goal for low-density lipoprotein (LDL) cholesterol (LDL-C) of lower than 70 mg/dl in patients with a very high risk (i.e. patients in secondary prevention) [1–3, 7–9]. On the other hand, it has been reported that patients with low TC and LDL-C plasma concentrations have a worse prognosis, in what is called the "cholesterol paradox", "reverse epidemiology" or "risk factor paradox or reversal" [10–14]. Nunes defined the "LDL cholesterol paradox" as a reduction in CVE risk related to a decrease in LDL-C blood concentration which is not concomitant with a decrease in total mortality [7]. Several possible causes are hypothesized to explain this risk factor reversal. On the one hand, better prognosis in patients with hypercholesterolemia may be related to (a) favorable effects of the "obesity paradox": improved hemodynamic stability in the obese, adipokine protection against tumor necrosis factor-α, lipoprotein protection against endotoxins, lipophilic toxin sequestration by adipose tissue, and the modulation of inflammatory processes [10]; (b) an earlier start of contact with health care professionals; and (c) the aforementioned evidenced favorable and pleiotropic effect of hypolipidemic drugs recommended for patients with prior diagnosed hyper-

cholesterolemia which is treated without meeting the recommended goals [1–3, 10]. On the other hand, the "cholesterol paradox" may be an effect of "reverse causality", in which poor prognosis in patients with low cholesterol blood concentration results not from the lack of the aforementioned favorable effects of hyperlipidemia, but from (d) unfavorable effects of comorbidities, such as systemic inflammation, malnutrition, malabsorption syndrome, neoplasm, end-stage liver disease, end-stage kidney disease, chronic obstructive pulmonary disease (COPD), and cardiac heart failure [15–18]; and/or (e) potential harmful effects of aggressive hypolipidemic therapy when hypercholesterolemia was diagnosed earlier and cholesterol was lowered too aggressively [7, 19]. Until now, the "cholesterol paradox" has been noted among geriatric patients [10] and in several acute (myocardial infarction [7, 11, 20, 21]) and chronic conditions, such as stable coronary artery disease, end-stage renal disease requiring dialysis, chronic heart failure, atrial fibrillation, peripheral artery disease, stroke, COPD, rheumatoid arthritis, and AIDS [4, 7, 13, 14–18, 22–27]. However, the prognostic importance of plasma lipid determination in the evaluation of the risk of all-cause in-hospital mortality and risk of readmission among consecutive inpatients has not been established. Therefore, we performed an analysis to answer this question.

Material and methods

We performed a historical prospective analysis of the electronic medical documentation of all non-selected, consecutive patients admitted to a university hospital during the course of 2 years, i.e. between July 1, 2014 and June 30, 2016. During this period, 70 076 hospitalizations were carried out, of which 64 856 (92.55%) concerned patients older than 18 years, and 53 375 (76.17%) lasted more than one day. Pregnant females hospitalized in the Department of Obstetrics were excluded from the study group. The remaining 34 191 (48.79%) patients underwent analysis. As the determination of plasma lipids in our hospital is not a routine aspect of patient management, their concentrations were not available for all patients, but only as follows: TC for 3 147/34 191 (9.20%) patients; LDL-C for 9 349 (27.34%); high-density lipoprotein (HDL) cholesterol (HDL-C) for 1 144 (3.35%); non-HDL cholesterol (non-HDL-C) for 1 051 (3.07%), and triglycerides (TG) for 7 845 (22.94%).

The following parameters were analyzed: age, gender, number of hospitalization days (length of in-hospital stay), hospitalization mode (whether urgent or scheduled), in-hospital all-cause mortality, non-scheduled readmission, Nutritional Risk

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Screen 2002 (NRS-2002) score (a score of at least 3 points in the questionnaire indicates a nutrition-related risk) [28], actual weight, height, body mass index (BMI), direct determination of TC, LDL-C (not calculated by use of the Friedewald formula), HDL-C, TG, and blood glucose. All the biochemical parameters included in the analysis (e.g. blood cholesterol and glucose concentration) were determined on the first day of hospitalization in a fasting state during respective hospitalizations.

Table I. Selected data in respective patient groups divided according to total cholesterol quartiles ($n = 3147$)

Parameter	TC < 133.28 mg/dl ($n = 787$; 25.01%)	$133.28 \leq$ TC < 176.20 mg/dl ($n = 788$; 25.04%)	$176.20 \leq$ TC < 214.90 mg/dl ($n = 787$; 25.01%)	TC $\geq$ 214.90 mg/dl ($n = 785$; 24.94%)
	1	2	3	4
Age [years]	65.55 ±17.27	54.81 ±18.33*	52.28 ±16.19*	53.51 ± 13.29*#
Male gender, n (%)	428 (54.38)	321 (40.74)*	237 (30.11)*#	246 (31.34)*#
BMI [kg/m²]	25.95 ±6.10	26.33 ±6.12	26.46 ±5.82	26.77 ±5.06*
Total cholesterol [mg/dl]	98.22 ±27.81	155.43 ±12.56*	195.32 ±11.06*#	260.95 ± 67.83*#+
LDL cholesterol [mg/dl]	67.35 ±22.20	94.61 ±17.52*	124.54 ±18.84*#	171.61 ± 37.37*#+
HDL cholesterol	35.79 ±13.80	50.82 ±16.27*	59.72 ±17.95*#	63.34 ±21.69*#+
Non-HDL cholesterol [mg/dl]	79.07 ±15.93	105.43 ±18.48*	135.84 ±21.02*#	187.97 ±41.52*#+
Triglycerides [mg/dl]	104.10 ±68.15	111.51 ±66.74*	120.91 ±64.74*#	195.86 ±385.89*#+
Fasting blood glucose [mg/dl]	145.26 ±75.95	119.23 ±66.68*	111.03 ±57.14*#	107.77 ±54.14*#
Number of patients with elevated troponin (> 0.014 ng/ml) blood concentration (n, % of patients with parameter determination due to clinical condition)	274 (75.14)	115 (50.22)*	71 (41.67)*	55 (38.19)*#
Number of hospitalizations with a diagnosis of cardiovascular disease on discharge, n (%)	179 (22.74)	151 (19.61)*	122 (15.50)*	111 (14.14)*#
Number of hospitalizations with a diagnosis of neoplastic disease on discharge, n (%)	124 (15.76)	52 (6.60)*	31 (3.94)*	22 (2.80)*#
Length of hospital stay [days]	17.13 ±17.38	8.32 ±8.91	6.10 ±6.63*#	5.62 ±6.99*#
Urgent admission, n (%)	614 (78.02)	404 (51.27)*	264 (33.55)*#	244 (31.08)*#
In-hospital all-cause mortality, n (%)	160 (20.33)	39 (4.95)*	14 (1.78)*#	5 (0.64)*#+
Risk of all-cause in-hospital mortality OR (95% CI)	14.22 (8.15–24.80)	2.90 (1.56–5.39)	1	0.36 (0.13–0.99)
Number of non-elective rehospitalizations within 14 days after discharge, n (%)	26 (3.30)	13 (1.65)*	3 (0.38)*#	6 (0.76)*
Number of non-elective rehospitalizations within 30 days after discharge, n (%)	51 (6.48)	27 (3.43)*	14 (1.78)*#	12 (1.58)*#
Number of non-elective rehospitalizations within 1 year after discharge, n (%)	100 (12.71)	65 (8.25)*	38 (4.83)*#	42 (5.25)*#

*Data presented as mean ± standard deviation or number of subjects (n) and %, as well as odds ratio (95% confidence interval) – OR (95% CI). Deficit of body mass was defined as a negative difference between actual and ideal body mass; % of fat mass, fat mass and fat-free mass were calculated from BMI; OR (95% CI) was calculated in relation to the third quartile of TC blood concentration. OR expresses the probability of the occurrence of in-hospital death in patients with a TC level above or below the third TC quartile; HDL cholesterol blood concentration was recognized as abnormal when in males it was below 40 mg/dl, and in females below 45 mg/dl. Percentage of patients in respective groups is related to the number of available data and not to the number of patients given in the heading. *Statistical significance of the difference between the first and the other columns (p < 0.05); #statistical significance of the difference between the second and third and fourth columns (p < 0.05); +statistical significance of the difference between the third and fourth columns (p < 0.05). TC – total cholesterol, BMI – body mass index, LDL – low-density lipoprotein, HDL – high-density lipoprotein, OR – odds ratio, CI – confidence interval.*

Data concerning treatment with lipid lowering were not available.

To evaluate the associations between the measured outcomes and the above-mentioned parameters in more detail, the following secondary parameters were also calculated:

- percentage of body fat was calculated according to the following formula: $(1.2 \times BMI) + (0.23 \times age) - (10.8 \times gender) - 5.4$, in which gender was accorded a value of "0" for females and "1" for males [29];
- "ideal weight" was calculated using the Lorentz formula [28];
- deficit of body mass was defined as a negative difference between actual and ideal body mass;
- quartiles of TC with their respective distribution of clinical characteristics (Table I);
- ranges of LDL-C according to goal values recommended by cardiovascular societies (< 70 mg/dl, 70–100 mg/dl, 100–115 mg/dl, ≥ 115 mg/dl) [1–3] (Table II).
- the percentage of patients with abnormal HDL-C blood concentration was calculated, defined as < 40 mg/dl for males and < 45 mg/dl for females [1–3] (Table III).

The main diagnoses on discharge were also noted. Cardiovascular diseases (CVD) as a cause of hospitalization were recorded by us when a patient was discharged, using the International Classification of Diseases 10th revision (ICD-10) diagnosis from group "I", with the exception of I84 and I85, as well as G45, G46, H34, H35, and H36. Malignant neoplasm as a cause of hospitalization was recorded when the final diagnosis on discharge was derived from ICD-10 group "C".

Measured outcomes

The following outcomes were measured: length of stay (LOS; duration of hospitalization (number of days hospitalized)), in-hospital all-cause mortality, and non-scheduled readmission (the second and subsequent hospitalizations during the period analyzed) in the 14-day, 30-day and 1-year periods following discharge. Every patient was identified on the basis of his or her personal identity number. In-hospital death was determined on the basis of information concerning outcome of hospitalization (died or discharged) which was available for every patients. When a patient was discharged and his or her personal identity number was repeated in our database, the date of the patient's discharge and readmission was checked. When the difference was shorter than 14 days, 30 days or one year respectively, the patient was recognized as being readmitted during 14 days, 30 days or 1 year, respectively. Emergency or scheduled hospitalization is always in-dicated by a leading doctor in the medical documentation of our hospitalization.

Bioethics

The investigation was conducted in compliance with the Declaration of Helsinki for medical research, after receiving permission from the local Bioethical Committee (No. 683/2016).

Statistical analysis

Statistical analysis was conducted using licensed versions of the statistical software Statistica (a data analysis software system), StatSoft, Inc. (2015), version 12. The normal distribution of the study variables was checked using the Shapiro-Wilk test. The results were mainly presented as the mean ± standard deviation, or n, %. The statistical significance of differences between groups was verified using Student's t-test and χ^2 test. The statistical significance level was set at a p-value < 0.05. The odds ratio (OR) was calculated according to the following formula: the product of the number of subjects with a measured outcome and the presence of the variables analyzed (exposed cases = patients who died in hospital and at admission had e.g. LDL-C ≥ 100 mg/dl) and the number of subjects without the measured outcome and analyzed variable (unexposed non-cases = e.g. patients with LDL-C blood concentration < 100 mg/dl who were discharged from hospital, i.e. survived hospitalization) divided by the product of the number of exposed non-cases and unexposed cases. The receiver operating characteristic (ROC) curve and area under the ROC curve (AUC) were also used to determine cut-off values for respective plasma lipids, which were then used for the OR calculation. Logistic regression using a quasi-Newton estimation method was applied to check the relationships between the qualitative measured outcomes and the clinical characteristics analyzed. Survival analysis using the Cox proportional hazard method was performed for the determination of independent variables determining survival duration during hospitalization (duration between admission and in-hospital death) and readmission-free survival during the 14- and 30-day and 1-year follow-ups. The following independent variables were included in the model: age, gender, NRS-2002 score, kind of therapy (conservative or operative), ratio of actual to ideal body weight, BMI, percentage of body fat calculated from BMI, diagnosis of CVD or neoplasm on discharge as a main disorder, fasting TC, LDL-C, HDL-C, TG and blood glucose concentration. Deficiencies in the variables due to the lack of a sufficient number of plasma lipid determinations and measured outcomes were addressed by using the mean values.

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Table II. Selected data in respective patient groups divided according to LDL cholesterol range (*n* = 9349)

Parameter	LDL < 70 mg/dl (*n* = 1329; 14.22%)	70 ≤ LDL < 100 mg/dl (*n* = 2659; 28.44%)	100 ≤ LDL < 115 mg/dl (*n* = 1229; 13.15%)	LDL ≥ 115 mg/dl (*n* = 4132; 44.20%)
	1	2	3	4
Age [years]	69.87 ±13.2	65.46 ±15.24*	63.60 ±15.94*#	60.52 ±14.5*#+
Male gender, *n* (%)	733 (55.15)	1 339 (50.36)*	545 (44.34)*#	1 847 (44.70)*#
BMI [kg/m²]	28.52 ±6.05	28.06 ±5.61*	27.56 ±5.74*#	27.68 ±5.25*#
Total cholesterol [mg/dl]	116.30 ±36.03	149.22 ±38.54*	175.02 ±19.35*#	228.10 ±47.52*#+
LDL cholesterol [mg/dl]	55.68 ±11.07	85.26 ±8.43*	107.42 ±4.22*#	152.54 ±31.69*#+
HDL cholesterol [mg/dl]	43.75 ±19.51	53.90 ±22.14*	54.42 ±20.64*	56.88 ± 17.16*#
Non-HDL cholesterol [mg/dl]	77.37 ±29.62	98.58 ±13.68*	119.70 ±10.54*#	166.31 ±38.29*#
Triglycerides [mg/dl]	104.10 ±128.83	114.21 ±87.34*	120.00 ±64.00*	149.29 ±96.35*#+
Fasting blood glucose [mg/dl]	137.33 ±75.03	124.84 ±58.28*	122.79 ±50.76*	120.78 ±55.84*#
Number of patients with elevated troponin (> 0.014 ng/ml) blood concentration (*n*, % of patients with parameter determination due to clinical condition)	423 (68.12)	657 (59.62)*	255 (53.91)*	794 (53.32)*#
Number of hospitalizations with a diagnosis of cardiovascular disease on discharge, *n* (%)	1 037 (78.03)	2 052 (77.17)	887 (72.17)*#	2 731 (66.09%)*#+
Number of hospitalizations with a diagnosis of neoplastic disease on discharge, *n* (%)	16 (1.20)	26 (0.98)	14 (1.14)	42 (1.02)
Length of hospital stay [days]	6.92 ±7.73	5.78 ±6.48*	6.05 ±7.43*	5.68 ±5.97*#
Urgent admission, *n* (%)	1 038 (78.10)	1 840 (69.20)*	841 (68.43)*	2 609 (63.14)*#+
In-hospital all-cause mortality, *n* (%)	54 (4.06)	56 (2.11)*	37 (3.01)*	59 (1.43)*#+
Risk for all-cause in-hospital mortality OR (95% CI)	1.56 (1.07–2.28)	1	1.14 (0.75–1.74)	0.53 (0.37–0.77)
Number of non-elective rehospitalizations within 14 days after discharge, *n* (%)	33 (2.48)	55 (2.07)*	20 (1.63)*#	60 (1.21)*#
Number of non-elective rehospitalizations within 30 days after discharge, *n* (%)	85 (6.40)	115 (4.32)*	51 (4.15)*	128 (3.10)*#
Number of non-elective rehospitalizations within 1 year after discharge, *n* (%)	282 (21.22)	424 (15.95)*	164 (13.34)*	479 (11.59)*#

*Data presented as mean ± standard deviation or number of subjects (n) and %, as well as odds ratio (95% confidence interval) – OR (95% CI). Deficit of body mass was defined as a negative difference between actual and ideal body mass; % of fat mass, fat mass and fat-free mass were calculated from BMI; OR (95% CI) was calculated in relation to the recommended LDL interval 70 ≤ LDL < 100 mg/dl. OR expresses the probability of the occurrence of in-hospital death in patients with an LDL value in the range above or below the reference range; HDL cholesterol blood concentration was recognized as abnormal when in males it was below 40 mg/dl and in females below 45 mg/dl. The percentage of patients in respective groups is related to the number of available data and not to the number of patients given in the heading. *Statistical significance of the difference between the first and other columns (p < 0.05); #statistical significance of the difference between the second and third and fourth columns (p < 0.05); +statistical significance of the difference between the third and fourth columns (p < 0.05). LDL – low-density lipoprotein, BMI – body mass index, HDL – high-density lipoprotein, CI – confidence interval, OR – odds ratio.*

Results

In our study, we analyzed the associations between plasma lipid levels and the outcomes measured among inpatients with a mean age of 59.88 ±17.52 years, mainly female (53.54%), who received conservative (59.27%) or operative (40.73%) treatment in hospitalizations across 13 wards of one university hospital during a 2-year period. Analysis of the relationships between
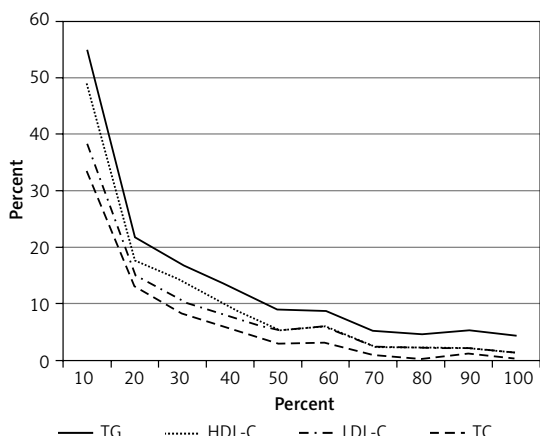
Table III. Selected data in respective patient groups divided according to the presence of recommended HDL cholesterol blood concentration

Parameter	Abnormal HDL-C (n = 336; 29.37%)	Recommended HDL-C level (n = 808; 70.63%)	P-value
Age [years]	57.53 ±17.14	53.80 ±16.09	0.001
Male gender, n (%)	170 (50.60)	242 (29.95)	0.001
BMI [kg/m^2]	28.64 ±6.51	26.56 ±5.43	0.001
Total cholesterol [mg/dl]	158.73 ±47.90	196.66 ±47.70	0.001
LDL cholesterol [mg/dl]	103.53 ±43.86	122.18 ±45.12	0.001
HDL cholesterol	32.44 ±8.53	62.75 ±16.08	0.001
Non-HDL cholesterol [mg/dl]	126.36 ±46.39	133.44 ±46.10	0.025
Triglycerides [mg/dl]	150.19 ±103.16	103.43 ±51.11	0.001
Fasting blood glucose [mg/dl]	123.95 ±59.08	107.93 ±53.75	0.001
Number of patients with elevated troponin (> 0.014 ng/ml) blood concentration (n, % of patients with parameter determination due to clinical condition)	93 (62.84)	103 (46.82)	0.003
Number of hospitalizations with a diagnosis of cardiovascular disease on discharge, n (%)	100 (29.76)	149 (18.44)	0.001
Number of hospitalizations with a diagnosis of neoplastic disease on discharge, n (%)	7 (2.08)	1 (0.12)	0.001
Length of hospital stay [days]	8.87 ±10.38	5.01 ±3.19	0.001
Urgent admission, n (%)	202 (60.12)	254 (31.44)	0.001
In-hospital all-cause mortality, n (%)	18 (5.33)	3 (0.37)	0.001
Risk of all-cause in-hospital mortality for patients with abnormal HDL cholesterol blood concentration in relation to counterparts OR (95% CI)	1.38 (0.77–2.49)		0.283
Number of non-elective rehospitalizations within 14 days after discharge, n (%)	9 (2.68)	4 (0.5)	0.001
Number of non-elective rehospitalizations within 30 days after discharge, n (%)	17 (5.06)	11 (1.36)	0.0001
Number of non-elective rehospitalizations within 1 year after discharge, n (%)	25 (7.44)	27 (3.34)	0.002

Data presented as mean ± standard deviation or number of subjects (n) and %, as well as odds ratio (95% confidence interval) – OR (95% CI). Deficit of body mass was defined as a negative difference between actual and ideal body mass. The percentage of fat mass, fat mass and fat-free mass were calculated from BMI. OR expresses the probability of the occurrence of in-hospital death of a patient with HDL cholesterol below the recommended range, which is ≥ 40 mg/dl for males and ≥ 45 mg/dl for females. The percentage of patients in respective groups is related to the number of available data and not to the number of patients given in the heading. HDL – high-density lipoprotein, BMI – body mass index, LDL – low-density lipoprotein, OR – odds ratio, CI – confidence interval.

plasma lipids and the prevalence of the outcomes measured shows that the poorest prognoses were for patients with the lowest plasma lipids levels located in the first two to three percentiles (Figure 1). We then performed a more detailed analysis of the associations between plasma lipids and the outcomes measured. As widely accepted goal values for TC are not available [1, 2], we checked the clinical importance of TC determination in relation to its quartiles (Table I). Approaching the analysis in this way confirmed the general conclusions from Figure 1: patients with a TC blood concentration from the lowest quartile had a 14-times greater risk than individuals with the TC plasma level located in the third quartile. Moreover, patients from the fourth TC quartile, with a TC blood concentration greater than 214.90 mg/dl, had a 64% lower relative risk of all-cause in-hospital mortality than their counterparts from the third TC quartile (Table I). However, the results presented in Table II were more surprising. Compared to individuals with an LDL-C level in the range 70 ≤ LDL < 100 mg/dl, patients with LDL-C < 70 mg/dl, which is recommended for patients with very high CVD risk [1–3], had a 56% greater risk of all-cause in-hospital death, and patients with LDL-C

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Percent	Total cholesterol (TC; n = 3147) [mg/dl]	LDL cholesterol (LDL; n = 9349) [mg/dl]	HDL cholesterol (HDL; n = 1144) [mg/dl]	Triglycerides (TG; n = 7845) [mg/dl]
10	98	63.7	30.5	60.6
20	123.5	76.6	37.3	73
30	142.8	87	42.8	84
40	160	97	47.5	95.3
50	176.2	108.3	52.4	107.7
60	191.1	120	57.4	122
70	207	133	62.5	139.5
80	226	148.8	69.8	164
90	256	171.2	79.5	208

Figure 1. All-cause in-hospital mortality occurrence in respective percentiles of plasma lipids

≥ 115 mg/dl had a 47% lower risk of in-hospital death. The mortality risk was even lower when patients with the highest LDL-C level were compared with those with LDL-C < 70 mg/dl, OR (95% CI; p): 0.34 (0.24–0.50; p < 0.001). Patients from the lowest range of LDL-C (Table II), similar to individuals with the lowest TC blood level (Table I), also had the highest prevalence of other measured outcomes and were more likely to have a CVD diagnosis on discharge. Patients in the lowest LDL-C range also had several other abnormalities, such as the highest average BMI, the largest average percentage of body fat, the highest percentage of individuals with abnormal HDL-C blood concentration and elevated troponin level, and the highest average fasting glucose concentration, which was greater than the cut-off value (126 mg/dl) for a diagnosis of diabetes mellitus (Table II). Analysis of Table II also shows poor LDL-C control among the hospitalized patients, because more than 60% of the patients from the respective LDL-C range ≥ 70 mg/dl had numerous CVD diagnoses, so the majority of them were high risk or very high risk CVD patients.

We also analyzed the clinical importance of inpatients having an abnormal HDL-C blood concentration on admission (Table III). We found that the majority of our inpatients (70.63%) had an HDL-C blood concentration that was in accordance with recommendations [1–3]. An abnormally low HDL-C blood concentration was related to older age, male gender, higher nutritional risk (NRS-2002), higher BMI, lower TC, higher TG, blood glucose and troponin, as well as greater prevalence of cardiovascular and neoplastic diseases on discharge. The prevalence of the measured outcomes was also higher in individuals with an abnormally low HDL-C blood concentration (Table III). Blood concentration of TG elevated above 150 mg/dl was associated with similar factors, but TC and LDL-C were higher and HDL-C blood concentration was lower in these subgroups, and the prevalence

of cancerous diseases and measured outcomes were similar in these dichotomized patient groups (data not presented).

To determine a cut-off value for patients' prognosis, we also determined ROC curves for the respective plasma lipids and outcomes measured (Figure 2). Next, we calculated the OR (95% CI) in split analysis in accordance with the determined cut-off values (Table IV). Total cholesterol and HDL-C had the strongest effect on reducing the risk of the outcomes measured. We also found that LDL-C level ≥ 73.1 mg/dl was associated with a reduction in measured outcomes risk, both in the whole of the group studied and in analysis limited only to patients with a CVD diagnosis on discharge (Table IV).

In multifactorial analysis, using a logistic regression model, we found blood concentration of TC, LDL-C and HDL-C to be significant, favorable, but weak factors affecting the risk of all the outcomes measured with average OR in the range 0.908–0.999 and a 95% CI of 0.875–0.999 (detailed data not presented). The strongest association was found for HDL-C in relation to all-cause in-hospital death, OR (95% CI): 0.080 (0.875–0.937). However, when the NRS-2002 score was added to the model, the effects of the plasma lipid variables were no longer significant. We also performed survival analysis using a Cox proportional hazards model. The influence of TC, LDL-C, HDL-C and TG was not statistically significant in any of these models concerning the respective measured outcomes (detailed data not presented).

Discussion

In our study, performed on a large, non-selected population of consecutive inpatients at a university hospital, the existence of a "lipid paradox" or "cholesterol paradox" was suggested only by univariate analysis. However, multivariate adjustment for clinical characteristics showed a neutral
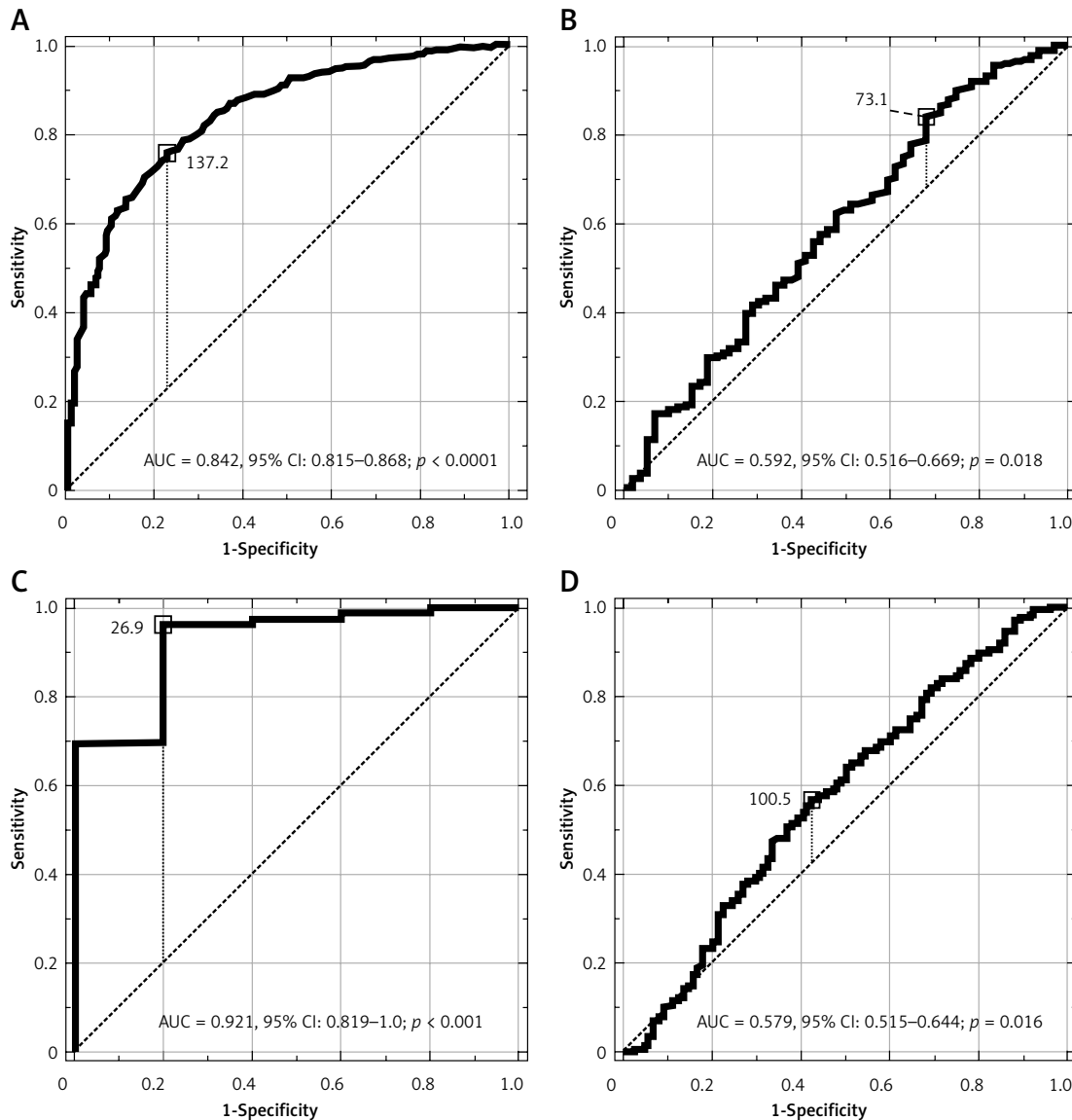
Figure 2. ROC curves for blood concentrations of respective plasma lipids as predictors for in-hospital all-cause mortality. **A** – ROC curve for TC and survival (Youden's index = 0.53, cut-off value: 137.20 mg/dl), **B** – ROC curve for LDL-C and survival (Youden's index = 0.16, cut-off value: 73.10 mg/dl), **C** – ROC curve for HDL-C and survival (Youden's index = 0.76, cut-off value: 26.90 mg/dl), **D** – ROC curve for TG and survival (Youden's index = 0.15, cut-off value: 100.50 mg/dl)

effect of plasma lipid levels on the risk of the outcomes measured, which suggests that this paradox is an effect of reverse causality, and higher blood cholesterol concentration is not a biomarker of better prognosis, but an effect of the better general condition of the patient and a lower severity of illness.

In many of our univariate analyses conducted in relation to plasma lipid quartiles (Table I) and ranges recommended by cardiological societies (LDL, HDL and TG, see Table II, Table III, Figure 1), as well as in relation to the cut-off values determined in ROC curve analysis (Figure 2), we found that patients with higher TC, LDL-C and HDL-C blood concentrations had a lower risk of all the outcomes measured than their counterparts, both

in the whole of the population studied and in the analysis limited only to patients with a diagnosis of CVD or cancer (Table IV). Our univariate analysis identified a worse prognosis for hospitalized patients with the lowest TC, LDL-C and TG, which, although contrary to findings in outpatient studies and in the general literature [1–3], corroborated results of recent, experimental, randomized and controlled trials. Recently, a few studies have failed to show a cardiovascular benefit of the aggressive lowering of LDL-C and raising of HDL-C blood concentration using cholesteryl ester transfer protein (CETP) inhibitors, evacetrapib [30], anacetrapib and dalcetrapib [31]. Torcetrapib even showed an increase in CVD events, despite an increase in HDL-C level [31]. These observations

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Table IV. Risk of the occurrence of the outcomes measured in relation to the cut-off values for respective plasma lipids determined in the ROC curves

Outcome measured	OR	95% CI	P-value
Total cholesterol ≥ 137.2 mg/dl:			
In-hospital all-cause death	0.10	0.06–0.13	< 0.001
14-day readmission after discharge	0.27	0.13–0.49	< 0.001
30-day readmission after discharge	0.33	0.23–0.50	< 0.001
1-year readmission after discharge	0.43	0.33–0.56	< 0.001
LDL cholesterol ≥ 73.1 mg/dl:			
In-hospital all-cause death	0.46	0.34–0.63	< 0.001
14-day readmission after discharge	0.66	0.46–0.96	< 0.001
30-day readmission after discharge	0.55	0.44–0.70	< 0.001
1-year readmission after discharge	0.57	0.50–0.66	< 0.001
LDL cholesterol ≥ 73.1 mg/dl (for patients with CVD diagnosis):			
In-hospital all-cause death	0.64	0.45–0.91	0.014
14-day readmission after discharge	0.66	0.43–0.99	0.045
30-day readmission after discharge	0.65	0.50–0.84	0.0012
1-year readmission after discharge	0.66	0.56–0.76	< 0.001
HDL cholesterol ≥ 26.9 mg/dl:			
In-hospital all-cause death	0.05	0.02–0.13	< 0.001
14-day readmission after discharge	0.10	0.0.3–0.31	< 0.001
30-day readmission after discharge	0.12	0.05–0.29	< 0.001
1-year readmission after discharge	0.19	0.09–0.38	< 0.001
Triglycerides ≥ 100.5 mg/dl:			
In-hospital all-cause death	0.72	0.56–0.92	< 0.001
14-day readmission after discharge	0.96	0.68–1.34	0.82
30-day readmission after discharge	0.95	0.76–1.14	0.42
1-year readmission after discharge	0.95	0.84–1.08	0.45

Data presented as the OR (95% CI). Split analysis was performed according to the cut-off values of respective lipid concentrations established in the ROC curve analysis. OR expresses the probability of the occurrence of the outcome measured in hospitalizations with a value of an analyzed plasma lipid higher than or equal to the established value. ROC – receiver operating characteristic, OR – odds ratio, CI – confidence interval, LDL – low-density lipoprotein, CVD – cardiovascular diseases, HDL – high-density lipoprotein.

raised doubts concerning the clinical importance of CETP inhibition [31], but may also show the lack of the assumed clinical importance of an increase in HDL-C and a large reduction in LDL-C. It is also possible that such aggressive therapy may lead to non-cardiovascular mortality, secondary to still undiagnosed adverse effects [7, 19], e.g. similar to statins, which cause a dose-dependent increase in the risk of diabetes mellitus [30, 32, 33].

Our univariate analysis revealed better outcomes in hospitalized patients with hyperlipidemia, which was also consistent with the results of observational studies. For example, Fruchter *et al.* [22], investigating retrospectively the rela-tionships between all-cause mortality and lipid profile and statin use in 615 patients after acute exacerbation of COPD, found, in a mean follow-up period of 24.8 months, in their multivariate analysis that blood TC concentration < 150 mg/dl (in our study this was 137.2 mg/dl, Figure 2, Table IV) was an independent risk factor for in-hospital death (hazard ratio (HR) 1.84; 95% CI: 1.25–2.71), despite finding a favorable effect of statins regardless of TC level. Wesley and Cox [26] demonstrated a U-shaped relationship between TC and mortality, although the authors suggested that these data should be interpreted with caution due to the potential effect of confounding

factors. Reddy *et al.* [21] found that inpatients with LDL-C < 77 mg/dl (the lowest quartile) had greater in-hospital all-cause mortality than individuals with an LDL-C blood concentration in the second, third or fourth quartile with adjusted OR 0.79, 0.80, and 0.85, respectively. In our study, the OR for risk of in-hospital death between patients with LDL-C < 70 mg/dl and LDL-C ≥ 115 mg/dl was 0.34. Reddy *et al.* [21] also found that patients in the lowest HDL-C cholesterol quartile (< 31 mg/dl) had greater risk of in-hospital mortality (OR = 1.20) compared with the highest HDL-C quartile (≥ 47 mg/dl). In our study, the OR for in-hospital death among patients with abnormal HDL-C levels compared to individuals with the recommended HDL-C level (≥ 40 mg/dl for males and ≥ 45 mg/dl for females) was 1.34 (Table III), and for HDL-C < 26.9 mg/dl (Figure 2) the OR was significantly greater (16.1) when the mortality risk associated with the HDL-C level mentioned was compared to subjects with HDL-C ≥ 26.9 mg/dl (Table IV). Cheng *et al.* [20] also confirmed the existence of a "cholesterol paradox" in 723 patients with acute myocardial infarction, showing that LDL-C blood concentration < 62.5 mg/dl and a TG level < 110 mg/dl were associated with an increased risk of in-hospital and 30-day mortality, with HR = 1.65 (95% CI: 1.18–2.30) and 5.05 (95% CI: 1.75–14.54), respectively.

However, the above-mentioned effects of higher blood lipid concentrations found in the univariate analysis disappeared in multifactorial analysis, when TC, LDL-C, HDL-C and TG influence on the prevalence of the outcomes measured was adjusted for age, cardiovascular and cancerous comorbidity and NRS-2002 score. NRS-2002 score might be considered as a marker both of nutritional status and severity of illness on admission because, in this questionnaire, body mass fluctuations, nutritional reserves, the amount and frequency of food eaten during the week prior to admission, and cause of hospitalization and place of treatment (intensive care unit or other) are taken into account [28]. The disappearance of a "cholesterol paradox" observed by us in the multivariate analysis after adjusting for clinical characteristics corroborates the results obtained by Cho *et al.* [34] and Wang *et al.* [12]. Cho *et al.* [34] analyzed in-hospital and 1- and 12-month clinical outcomes after percutaneous coronary intervention (PCI) in 9 571 eligible patients with acute myocardial infarction from the Korea Acute Myocardial Infarction Registry. Despite finding in the univariate analysis that clinical outcome occurrence was lower when LDL-C increased, in multivariate analysis using a Cox proportional hazards model they failed to confirm the significance of LDL-C as an independent predictor of mortality at 12 months,

and concluded from their data that a "cholesterol paradox" in patients with acute myocardial infarction is related to confounding by baseline characteristics associated with survival. Similar conclusions were reported by Wang *et al.* [12], who, in 84 429 patients from a registry of non-ST-segment elevation acute coronary syndromes, found significantly lower in-hospital mortality in those with a history of hypercholesterolemia (unadjusted OR (95% CI): 0.58 (0.55–0.62); after adjusting for baseline characteristics: OR (95% CI): 0.71 (0.66–0.76)), and prior statin use: OR (95% CI) 0.74 (0.68–0.80). This "cholesterol paradox" was still apparent in a crude analysis when the authors excluded patients with a history of hypercholesterolemia from the analysis and restricted it to individuals with newly diagnosed elevated LDL-C ≥ 100 mg/dl, OR (95% CI): 0.58 (0.50–0.67), although its statistical significance disappeared after multivariable adjustment, OR (95% CI): 0.86 (0.73–1.01).

Although we obtained a number of statistically significant results, we could not avoid several limitations, which may influence the strength and clinical importance of the deduction based on our results. Firstly, the prevalence of death and non-elective readmissions found might be biased by the accumulation of seriously ill and malnourished patients who needed hospitalization, although other studies analyzing in-hospital mortality were affected by the same bias. One of the purposes of our study was to determine whether routine blood lipid determination could help in risk stratification in hospitalized patients, regardless of clinical condition and prior medication (e.g. with statins or fibrates). Therefore, our observations are relevant only for consecutive inpatients, not for outpatients. Secondly, in our study, both short-term and long-term follow-up are lacking, although an analysis of readmission risk can be considered their equivalent. Thirdly, we only analyzed non-elective rehospitalizations in our hospital. However, our patients might have been admitted to other medical centers, which was not noted, and may have biased our results. Fourthly, in our study, we only analyzed all-cause mortality, without consideration of disease- and lifestyle- (e.g. smoking, alcohol or drug misuse) specific risk of death. The greater prevalence of cardiovascular and neoplastic diseases, as well as the percentage of patients with an NRS-2002 score ≥ 3 between the first and remaining TC quartiles (Table I), might have affected the differences observed in mortality and readmissions between the respective groups. Similar limitations concerned LDL-C (Table II) and HDL-C (Table III). The importance of these shortcomings is confirmed in the multivariate analysis, although, due to the lack of avail-

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ability of all the required determinations and the necessity of addressing this by using the mean value, the results of our survival analysis should also be interpreted carefully. Fifthly, our analysis was performed retrospectively on the basis of electronic documentation and, therefore, some clinical data and medication might have been overlooked.

In conclusion, a statistically significant effect of a "cholesterol paradox" linking a better prognosis with higher blood lipid concentrations was found only in the unadjusted analysis, but, after adjustment for clinical characteristics in multivariate analysis, the plasma lipid levels had a neutral influence on the occurrence of the outcomes measured. This suggests that a low blood cholesterol level should be interpreted as a biomarker of a patient's illness severity, and risk of unfavorable outcomes during hospitalization, and not as an indication for, for example, stopping treatment with statins.

Conflict of interest

The authors declare no conflict of interest.

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