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Prognostic impact of plasma lipids in patients with lower respiratory tract infections – an observational study

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Summary

Principles: A decrease in plasma lipids occurs during severe sepsis and has prognostic implications in critical illness. Whether lipids have prognostic implications or could help to differentiate community-acquired pneumonia from other lower respiratory tract infections remains unknown.

Methods: We analysed data from patients with lower respiratory tract infections enrolled in four prospective trials. We studied the time courses of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) and compared them with the underlying diagnosis and medical outcomes.

Results: Of 572 patients included, 372 had community-acquired pneumonia and 200 acute and exacerbations of chronic obstructive bronchitis. We found significantly lower concentrations of TC, LDL-C and HDL-C in all patients on admission as compared to hospital discharge, particularly in community-acquired pneumonia. A multivariate logistic regression analysis including HDL-C, CRP, age and diabetes showed that HDL-C (OR: 0.18 [95%CI 0.11–0.3]) and CRP (OR: 1.01 [95%CI 1.01–1.02]) were independent predictors of community-acquired pneumonia. TC levels were significantly lower in non-survivors than in survivors (3.26 mmol/L [95%CI 2.58–3.96] vs 3.78 mmol/L [95%CI 3.01–4.65]). The prognostic accuracy, defined as the area under the receiver operator characteristic curve of TC to predict mortality, was 0.63 (95%CI 0.53–0.72) in all patients and increased to 0.94 (95%CI 0.86–1.00) in patients with bacteraemic community-acquired pneumonia.

Conclusions: In conclusion, low lipid levels, particularly low HDL-C, pointed to bacterial infection and low TC was predictive of adverse outcomes in patients with lower respiratory tract infections. Reflecting the severity of disease, plasma lipid levels may be a complementary tool in the diagnostic and prognostic workup of patients with lower respiratory tract infections.

Key words: lipid levels; cholesterol; sepsis; prognosis; pneumonia

Introduction

Severe illness affects plasma lipid levels. In critically ill and septic patients decreased circulating levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) have been reported, while serum triglyceride (TG) levels were increased [1–5]. In addition, HDL-C concentrations were significantly lower in severely ill patients from a medical intensive care unit if an infection was present, and correlated with medical outcomes independently of the underlying diseases [2, 3, 6]. Likewise, in children with severe meningococcal sepsis, HDL-C and LDL-C levels on admission were inversely associated with disease severity and mortality [5]. However, whether in patients with less severe systemic infections plasma lipids have prognostic implications, or could help to differentiate bacterial from nonbacterial infection, remains unknown.

Lower respiratory tract infection (LRTI) summarises a broad and continuous spectrum of diseases including viral bronchitis and community-acquired pneumonia (CAP). Viral bronchitis causes lung tissue damage and increases suscepti-

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bility to bacterial superinfection. Bacterial CAP is the most important precursor of sepsis and the major infection-related cause of death [7]. In the absence of chest x-rays, clinical signs and symptoms of CAP and routine laboratory tests are not specific and sometimes misleading [8, 9]. Diagnostic markers discriminating bronchitis from CAP facilitate the diagnostic workup of patients and provide guidance for antimicrobial treatment [10–14]. In addition, assessment of disease severity and prediction of outcome in patients with LRTI is crucial for decision-making on patient management, such as the need for hospital or intensive care admission and suitability for hospital discharge [14, 15].

In this study we compare plasma concentrations of plasma lipids in 572 patients with LRTI and study the diagnostic and prognostic impact of TC, LDL-C, HDL-C and TG.

Material and methods

Setting and study population

Data from four prospective studies enrolling patients between December 2002 and April 2007 with diagnosed LRTI, who presented to the emergency department of a 950-bed tertiary care centre in Basel, Switzerland, were pooled and analysed [10, 12–14]. The design of the trials was similar, and a complete detailed description can be found elsewhere [10, 12–14]. In brief, in all trials consecutive patients with LRTIs including acute and exacerbation of chronic obstructive bronchitis (COPD) and asthma, and CAP, were randomly assigned to procalcitonin (PCT)-guided antibiotic therapy or to standard treatment according to guidelines. The aim of all trials was to study the impact of procalcitonin-guided antibiotic treatment. The first three trials studied antibiotic exposure in different LRTI entities as the primary endpoint, while the fourth study was powered to demonstrate non-inferiority for adverse medical outcomes in a multicentre design. For this last trial only patients from University Hospital Basel were included. For all studies, CAP was defined as the presence of a new infiltrate on the chest radiograph accompanied by one or more acquired acute respiratory symptoms and signs such as cough, sputum production, dyspnoea, fever above 38.0 ºC, auscultatory findings of abnormal breath sounds and rales, leucocytes higher than $1x10^{10}$ cells/L, or leukopenia below $4x10^{9}$ cells/L [15]. Exacerbation of COPD was defined by post-bronchodilator spirometric criteria according to the GOLD guidelines as a FEV1/FVC ratio below 70%, and severity categorised according to GOLD criteria [16, 17]. Acute bronchitis was defined as LRTI in the absence of underlying lung disease or focal chest signs or infiltrates on chest x-ray respectively [18]. Patients with cystic fibrosis, active pulmonary tuberculosis, hospital-acquired pneumonia and severe immunosuppression were not eligible for inclusion.

Patients were examined on admission to the emergency department by a medical resident supervised by a board-certified specialist in internal medicine. Baseline assessment included collection of clinical data and vital signs, comorbid conditions and routine blood tests. The laboratory workup for patients with CAP included blood cultures and collection of urine samples for detection of *Legionella pneumophila* [12].

All trials were approved by the local ethical committees and registered in the Current Controlled Trials Database. All patients gave written informed consent.

The intention of this post hoc analysis was to study the value of plasma lipids in assessing prognosis, severity and differentiation of CAP from other etiologies in a well defined cohort of patients with diagnosed LRTI. For the purpose of this analysis we used available clinical and laboratory data of a subset of 572 out of a total of 853 patients (67%) in whom plasma lipids including TC, HDL-C, LDL-C and TG concentrations were measured on admission and during follow up as part of the routine laboratory workup. Records of all patients included were reviewed to retrieve complete laboratory data on admission, on day 3–5 and on hospital discharge, and additional information on comorbidities and comedications which potentially influence plasma lipid levels, such as the presence of diabetes or statin and corticosteroid use. To compare lipid levels with other well known markers of inflammation, we used C-reactive protein (CRP) and albumin concentrations from the routine laboratory assessment.

Outcome

Adverse medical outcome for this analysis was defined as a need for intensive care unit (ICU) admission during index hospitalisation, and death from any cause until follow-up. Patients who survived until follow-up were counted as survivors, and patients who died within the follow-up period as non-survivors.

Statistical analysis

The manuscript was prepared according to the STROBE statement [19]. Discrete variables are expressed as counts (percentage) and continuous variables as medians and interquartile ranges (IQR) unless stated otherwise. Frequency comparison was performed by chisquare tests. Two-group comparison of normally distributed data was performed by Students t-test. For multigroup comparisons, one-way analysis of variance with least square difference for posthoc comparison was applied. For data not normally distributed, the Mann-Whitney-U test was used if only two groups were compared, and Kruskal-Wallis one-way analysis of variance if more than two groups were compared. Logistic regression models and receiver-operating-characteristics (ROC) with sensitivities and specificities for different cutoff values were calculated using STATA 9.2 (Stata Corp, College Station, Tex). Thereby, outcomes were either survival until follow-up or adverse medical outcome including need for ICU admission and death until follow-up respectively. Correlation analyses were performed using Spearman rank correlations. All testing was two-tailed and p values below 0.05 were considered to indicate statistical significance.

Results

Baseline parameters

Of the 572 patients included, 372 had CAP and 200 had other LRTI including bronchitis (n = 23), exacerbation of COPD (n = 173) and exacerbation of asthma (n = 4). The median age of the patients (334 men and 238 women) was 74 years (IQR 65–82). Ear temperature ≥38 °C was present in 50% of patients. Overall, 93% of patients had relevant comorbidities including COPD (52%), cardiopathy (61%), hypertension (65%), neoplastic disease (26%), renal disease (34%) and diabetes mellitus (22%). On admission, 120 patients (22%) were treated with statins and 30 patients (5%) were on systemic corticosteroid medication. In 224 (39%) and 272 (48%) patients systemic and/or inhalative steroids were started on admission as part of disease management. Detailed patients' characteristics are summarised in table 1.

A systemic inflammatory response syndrome (SIRS) as defined by the American College of Chest Physicians and the Society of Critical Care Medicine [20] was found in 70% of the patients (4, 3 and 2 criteria in 56, 149 and 195 patients respectively). Bacteraemic CAP was diagnosed in 40 patients (7.0%), where growth of bacteria in blood cultures was documented (*Streptococcus pneumoniae* [75%], *Staphylococcus aureus* [7.5%], *Escherichia coli* [7.5%], *Klebsiella pneumoniae [5*%], others [5%]).

Table 1

Baseline characteristics of the 572 patients with lower respiratory tract infections separated into patients with community-acquired pneumonia (CAP) and patients with other lower respiratory tract infection than community-acquired pneumonia (non-CAP LRTI).
COPD: Chronic Obstructive Pulmonary Disease, ICU: Intensive Care Unit.

	CAP (n = 372)	Non-CAP LRTI (n = 200)	p-value
Demographics			
Age**	71.4(15.8)	72.1(10.5)	0.5
Male sex - no. (%)	226(61)	108(54)	<0.0001
Coexisting illnesses – no. (%)			
COPD	117(31.5)	177(88.5)	<0.0001
Cardiopathy	223(59.9)	125(62.5)	0.6
Diabetes mellitus	76(20.4)	47(23.5)	0.3
Renal dysfunction	136(36.5)	57(28.5)	0.04
Neoplastic disease	97(26.1)	51(25.5)	0.8
Hypertension	232(62.4)	139(69.5)	0.1
Clinical examination			
Confusion – no. (%)	20(5.4)	1(0.5)	0.86
Systolic blood pressure* mm Hg	130(25)	139(24)	<0.001
SIRS Criteria – no. (%)			
Respiratory rate >20 bpm	197(52.9)	106(53.0)	0.06
Pulse >90 bpm	231(62.1)	112(56.0)	0.9
Temperature >38 °C, <36 °C	222(59.7)	54(27.0)	0.02
Leukocyte count >12, <4	197(52.9)	77(38.5)	0.3
Laboratory findings*			
C-reactive protein (mg/L)	142(64-229)	27(9-61)	<0.0001
Leukocyte count (x109)	12.1(8.9-16.0)	10.6(8.3-13.7)	0.001
Albumin (g/L)	30(26-33)	34(30-37)	<0.0001
Glucose (mmol/L)	7.2(6.2-8.5)	7.4(6.2-9.1)	0.3
Medication on admission – no. (%)			
Statins	70(18.8)	50(25.0)	0.1
Inhalative steroids	107(28.7)	165(82.5)	<0.0001
Systemic steroids	10(2.7)	20(10.0)	0.1
Outcomes – no. (%)			
Death	30(8.1)	8(4.0)	0.06
ICU	54(14.5)	25(12.5)	0.1
ICU or death	75(20.2)	30(15.0)	0.1
Length of Hospital stay (days)*	13(9-18)	14(10-18)	0.6

* Median (Interquartile Range, IQR); ** mean and standard deviation (SD)

Outcomes

Adverse medical outcomes were observed in 97 patients, including 71 admissions to the ICU and/or 38 deaths. All patients in this analysis were treated as inpatients with a median hospital stay of 13 days (IQR 9-18).

Lipid levels on admission and follow up

In all patients with LRTI, significantly lower levels of TC (p <0.0001), LDL-C (p <0.0001) and HDL-C (p <0.0001) were found on admission as compared to hospital discharge. Changes of plasma lipids were more pronounced in patients with CAP and particularly in bacteraemic CAP (fig. 1). These changes were also observed for acute phase proteins such as CRP and less pronounced for albumin.

Diagnostic value of lipid levels on admission

To study whether plasma lipids could differentiate viral LRTI from CAP, patients were separated into CAP (n = 332), blood culture positive (bacteraemic) CAP (n = 40) and other LRTI (n = 200) including exacerbation of acute and chronic

Table 2

(a) Prediction of community-acquired pneumonia (n = 372) and (b) prediction of bacteraemia (n = 40) in patients with lower respiratory tract infections (n = 572) using multivariate regression analysis. Odds Ratio, 95% Confidence Interval (95%CI) and p-values are displayed.

a) Predictor	Odds ratio (95% CI)	P-value
HDL-C	0.18 (0.11–0.30)	<0.0001
C-reactive protein	1.01 (1.01–1.02)	<0.0001
Statin use	0.89 (0.51–1.53)	0.7
Diabetes	0.87 (0.51–1.51)	0.6

b) Predictor	Odds ratio (95% CI)	P-value
HDL-C	0.36 (0.14–0.96)	0.04
C-reactive protein	1.001 (1.001–1.008)	<0.01
Statin use	0.53 (0.17–1.63)	0.3
Diabetes	1.23 (0.51–3.18)	0.6

bronchitis and asthma. On admission patients with CAP had significantly lower TC (p <0.0001), LDL-C (p <0.0001) and HDL-C (p <0.0001), and a higher TG concentration (p <0.0001) as compared to non-CAP patients. These changes were more pronounced in patients with blood culture positive CAP. Conversely, on hospital discharge TC, LDL-C, HDL-C and TG levels were similar in CAP and other LRTI patients.

Correlation analysis showed a significant negative correlation of the acute phase protein CRP with HDL-C (r^2 = –0.25) and a positive correlation with albumin (r^2 = 0.24), and only weak correlations with LDL-C, TC and TG. In addition, there was a weak correlation between HDL-C and the CURB-65 score (r = 0.17, p = 0.001) and the pneumonia severity index (r = 0.11, p = 0.04) [21, 22].

To investigate whether plasma lipids were able independently to discriminate CAP from other LRTI, and bacteraemic CAP from non-bacteraemic CAP respectively, we calculated multivariate regression logistic models entering each single lipid value, CRP, the presence of diabetes and statin use as covariates. HDL-C was the best discriminator of CAP from other LRTI (OR: 0.18, p <0.0001) and the best predictor of bacteraemic CAP (OR: 0.36, p = 0.04). Table 2 shows the respective odds ratios and significance levels of all covariates.

To assess the overall diagnostic accuracy of the different parameters to differentiate CAP from other LRTI, we calculated receiver operating characteristics (ROC) curve analyses. Of all plasma lipids, HDL-C had the highest diagnostic accuracy to diagnose CAP (AUC: 0.82 [95%CI 0.78–0.85]) and to predict bacteraemia (AUC: 0.74 [95%CI 0.65–0.83]), which was within the range of CRP (AUC: 0.85 [95%CI 0.82–0.88], p = 0.14 and AUC: 0.73 [95%CI 0.65–0.81], p = 0.77) and significantly higher as compared to leucocytes. Details of the ROC statistics are presented in table 3.

Table 3

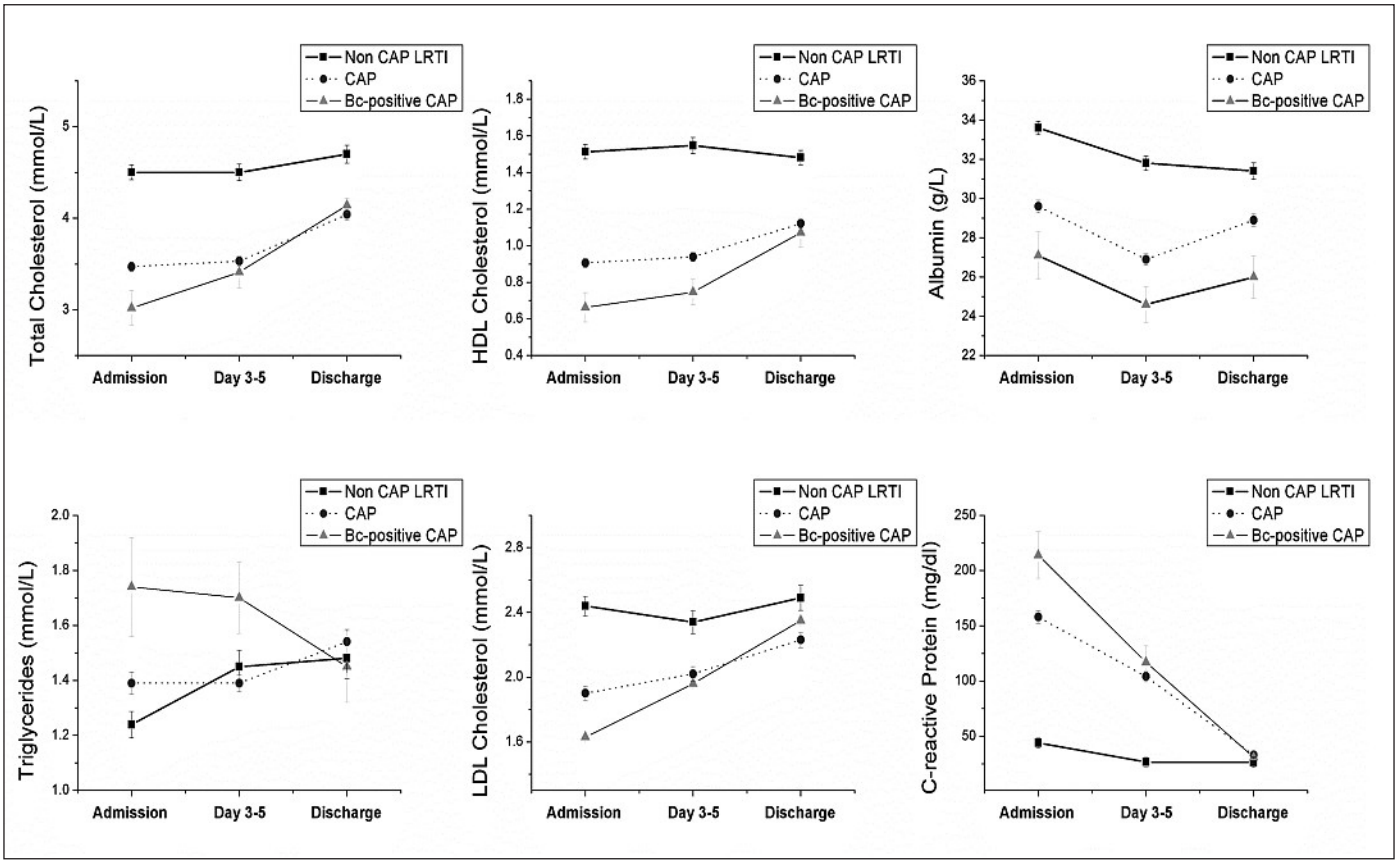
Receiver operating characteristic (ROC) plot analysis of different laboratory parameters with respect to prediction of (a) community acquired pneumonia (CAP) and (b) bacteraemia. The p values correspond to the difference between the area under the curve (AUC) of the parameters and the AUC of CRP.
AUC: area under the curve; CI: confidence interval.

a) Parameter	AUC	95% CI	P-value
C-reactive protein (mg/dl)	0.85	0.82–0.88	
HDL-C (mmol/L)	0.82	0.78–0.85	0.14
TC (mmol/L)	0.78	0.74–0.82	<0.01
LDL-C (mmol/L)	0.68	0.64–0.73	<0.0001
TG (mmol/L)	0.59	0.54–0.64	<0.0001

b) Parameter	AUC	95% CI	P-value
C-reactive protein (mg/dl)	0.73	0.65–0.81	
HDL-C (mmol/L)	0.74	0.65–0.83	0.77
TC (mmol/L)	0.70	0.61–0.78	0.78
LDL-C (mmol/L)	0.67	0.58–0.76	0.39
TG (mmol/L)	0.62	0.52–0.71	0.01

Figure 1

Mean levels of plasma lipids, albumin and C-reactive protein (CRP) on admission, after 3–5 days and on hospital discharge in patients with community-acquired pneumonia (CAP), blood culture positive CAP and other respiratory tract infections (nonCAP).
Error bars represent standard error of the mean (SEM). Dashed lines represent normal values.



At an HDL-C cutoff of 0.6 mmol/L, the sensitivity (specificity) to diagnose CAP and positive blood cultures was 80% (67%) and 91% (36%), with a positive likelihood ratio of 0.11 and 0.29. Conversely, the specificity (sensitivity) at a cutoff of 2.0 mmol/L to exclude CAP and positive blood culture was 80% (62%) and 58% (56%) negative likelihood ratio of 9.8 and 3.4 respectively. ROC curve analysis of plasma lipids and CRP to predict positive blood cultures in the subgroup of patients with CAP revealed similar results, particularly non-significant differences between HDL-C and CRP.

Lipid levels on admission as prognostic indicators for outcome

We assessed the predictive value of plasma lipids on admission to predict death and adverse medical outcome (death and/or ICU admission) respectively. Patients with not surviving LRTI had similar HDL-C and TG levels on admission to survivors, but significantly lower TC (3.26 % [IQR: 2.58–3.96] vs. 3.78 [IQR: 3.01–4.65], p <0.01) and LDL-C (1.74 [IQR: 1.04–2.43] vs 2.07 [IQR: 1.52–2.62], p <0.05) concentrations. Likewise, patients with adverse medical outcome had lower TC (p = 0.03) and LDL-C (p = 0.04) and similar HDL-C (p = 0.18) and TG (p = 0.14) concentrations. A multivariate logistic regression analysis including the presence of diabetes, statin use and CRP as covariates showed that TC and LDL-C, but not CRP, were each independent predictors for mortality (OR: 0.63 [95%CI: 0.45–0.90], p = 0.01 and OR: 0.56 [95%CI: 0.35–0.90] p = 0.02). A similar analysis showed that lipid concentrations were not predictive of adverse medical outcome. A ROC curve analysis revealed AUCs of 0.63 (95%CI: 0.53–0.72) and 0.60 (95%CI: 0.50–0.71) for TC and LDL-C to predict death and AUCs of 0.57 (95%CI 0.50–0.63) and 0.56 (95%CI 0.50–0.63) for TC and LDL-C to predict death and need for ICU admission.

In addition, we repeated the same analysis including only patients with CAP with and without bacteraemia respectively. The prognostic accuracy in the subgroup of CAP patients was similar to all LRTI patients. In bacteraemic patients, however, the AUC of LDL-C and TC increased to 0.94 (95%CI: 0.82–1.00) and 0.96 (95%CI: 0.89–1.00).

Discussion

This study investigated changes in plasma lipid levels in patients with LRTI, and particularly whether plasma lipids were different in bacterial and non-bacterial LRTI, and whether they have prognostic implications. We found markedly lower levels of TC, LDL-C and HDL-C on admission, with recovery until discharge in patients with LRTI. These changes were most pronounced in patients with CAP, especially those with bacteraemia. In a multivariate regression analysis HDL-C showed high diagnostic accuracy in differentiating CAP from other LRTI, and predicted subsequent bacteraemia in patients with CAP. In addition, low TC and LDL-C, but not low HDL-C concentrations, were independent predictors of short-term mortality in LRTI, with high prognostic accuracy in bacteraemic patients.

The exact pathophysiological mechanisms underlying hypocholesteraemia in severe illness and sepsis have never been fully understood [23]. Different mechanisms, including dysbalance between synthesis and utilisation of plasma lipids, usage of lipids to restore damaged cell membranes, and interaction of cytokines and bacterial toxins with lipids, have been discussed [3, 23–31]. Clinical and experimental studies demonstrated that high circulating levels of cytokines decrease cholesterol levels during severe infection [18–26]. Antiinflammatory and anti-oxidative properties of HDL-C were described [3, 29–31]. One important mechanism leading to the decrease in HDL-C is consumption through bacterial substances, particularly lipopolysaccharide (LPS) and other endotoxins. Thus, lipids are used as a scavenger mechanism of host defence because cholesterol and lipoproteins mediate LPS clearance through detoxification, forming complexes and neutralising its toxic effects [25–28]. In addition, lipoproteins bind a wide variety of enveloped and non-enveloped DNA and RNA viruses and are involved in the defence against several parasites [27, 28].

In accordance with these experimental findings the present study demonstrates that in unselected patients with less severe systemic infections cholesterol values on admission are significantly altered depending on disease severity. Remarkably, this clinical study demonstrates that plasma lipids correlate with the likelihood of bacterial LRTI and growth of bacteria in blood cultures. If confirmed in further studies and combined with other prognostic clinical and laboratory markers, measurement of plasma lipids may allow clinicians to target patients with pneumonia in whom blood cultures are most likely to yield a pathogen [32–37]. The variation during the hospital stay and the correlation of HDL-C with albumin and C-reactive protein suggests that HDL-C is a dynamic surrogate marker of systemic infections [38]. Keeping this in mind, physicians should be reminded that measurement of cholesterol values in patients with LRTI and systemic infections should not be used for cardiovascular risk prediction, since circulating levels of TC, LDL-C and

HDL-C may be false-low and levels of TG may be false-increased respectively.

In critically ill patients, changes in cholesterol levels, and particularly a decrease in HDL-C, have been put forward as a predictor of severity of illness and adverse medical outcome by some investigators [1, 2, 6, 23], while other studies could not confirm this association [4, 39]. In our study of patients with less severe disease, we found a modest difference in TC and LDL-C, but not in HDL-C and TG, between survivors and non-survivors. Subgroup analysis revealed that these differences were only present in patients with CAP, and especially in bacteraemic patients, where they displayed high prognostic accuracy in predicting short-term mortality. Importantly, in multivariate regression analysis these changes were independent of underlying diabetes and statin use, two conditions known to affect lipid metabolism. Accurate assessment of disease severity and prediction of outcome are prerequisites for safe decision-making on in- and outpatient management in patients with CAP. In the ICU setting, measurement of cholesterol values has been shown to improve risk prediction, and inclusion of lipid values in clinical risk assessment scores of critically ill patients has been advocated [6]. Based on the results of this study, measurements of TC and LDL-C may improve risk prediction in bacteraemic patients with CAP.

Some limitations should be considered in the interpretation of the present results. First, a true gold standard for the differentiation of viral and bacterial LRTI is lacking, as infiltrates on chest radiographs may be unspecific, and isolation of causative microorganisms in blood cultures is possible only in a minority of patients [40]. We therefore separated patients into three different groups, namely CAP, bacteraemic CAP and non-CAP LRTI. Second, it may be argued that the diagnostic accuracy of plasma lipids should be compared to serum procalcitonin rather than CRP. However, as this analysis takes advantage of patients included in intervention studies stratifying patients on procalcitonin values, we believe this analysis would be biased in a non-conservative way. Third, the number of outcome events in this study to assess the prognostic accuracy of lipid levels in regression models was rather low, thus limiting the generalisabilty of the results. Fourth, we included only patients who had at least two plasma lipid measurements during the hospital stay, and hence this cohort is only representative of hospitalised patients with LRTI. Fifth, the study presented is a post-hoc analysis of patients included in prospective studies at a single institution. So we interpret our results rather as hypothesis-generating than definitive.

Nevertheless, to our knowledge this is the first report investigating diagnostic and prognostic implications of plasma lipids in a well defined cohort of patients with LRTI, and is thus noteworthy.

In conclusion, low levels of plasma lipids, particularly low HDL-C, pointed to a bacterial infection and low TC was predictive of adverse outcomes in patients with LRTI. In addition to cardiovascular risk prediction, plasma lipid levels may be a helpful tool in the diagnostic and prognostic workup of patients with respiratory tract infections.

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