

Hyperlipidaemia and mortality among patients hospitalised with pneumonia: retrospective cohort and propensity score matched study

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ABSTRACT

Objective To characterise the potential association of hyperlipidaemia (HLP) versus no HLP with all-cause mortality among patients hospitalised for pneumonia.

Design Propensity score matched retrospective study.

Participants The study cohort consisted of consecutive 8553 adults hospitalised at a large academic centre with a discharge diagnosis of pneumonia from 1996 through 2015, followed until death or end of the study period, 17 August 2017.

Outcomes The outcome was HR for mortality at 28 days and in the long term in patients with pneumonia with concurrent HLP compared with those with no HLP. We first constructed multivariable Cox proportional regression models to estimate the association between concurrent HLP versus no HLP and mortality after pneumonia hospitalisation for the entire cohort. We then identified 1879 patients with pneumonia with concurrent HLP and propensity score matched in a 1:1 ratio to 1879 patients with no HLP to minimise the imbalance from measured covariates for further analysis.

Results Among 8553 unmatched patients with pneumonia, concurrent HLP versus no HLP was independently associated with lower mortality at 28 days (HR 0.52, 95% CI 0.41 to 0.66) and at a median follow-up of 3.9 years (HR 0.75, 95% CI 0.70 to 0.80). The risk difference in mortality was consistent between 1879 propensity score matched pairs both at 28 days (HR 0.65, 95% CI 0.49 to 0.86) and at a median follow-up of 4 years (HR 0.88, 95% CI 0.81 to 0.96). In the subgroup of patients with clinically measured low-density lipoprotein cholesterol (LDL-C), graded inverse associations between LDL-C levels and mortality were found in both unmatched and matched cohorts.

Conclusions Among hospitalised patients with pneumonia, a diagnosis of HLP is protective against both short-term and long-term risk of death after adjustment for other major contributors to mortality in both unmatched and propensity score matched cohorts. These findings should be further investigated.

INTRODUCTION

Hyperlipidaemia (HLP) is a major modifiable risk factor for the development of atherosclerotic cardiovascular disease in the general

Key messages

- ▶ Effect of hyperlipidaemia on mortality after hospitalization for pneumonia is not fully understood.
- ▶ We examined the association of hyperlipidaemia with short-term and long-term mortality after hospitalisation for pneumonia in a large cohort of patients with hyperlipidaemia who were matched to no hyperlipidaemia for baseline characteristics using a propensity score matching method.
- ▶ The present study highlights the mortality benefit of hyperlipidaemia in patients with pneumonia, and if confirmed in larger and wider patient populations will have potential clinical implication for the treatment of concurrent hyperlipidaemia among patients with pneumonia.

population,^{1–3} and lipid-lowering by statin therapy decreases the risk of cardiovascular mortality.^{4–7} In clear distinction from the general population where low-density lipoprotein cholesterol (LDL-C) increases cardiovascular risk, elevated serum cholesterol is increasingly related to reduced morbidity and mortality in patients with sepsis from diverse conditions. Early experimental studies found that LDL promotes clearance of bacterial toxins and therefore may be advantageous in patients with sepsis and some other conditions.^{8,9} Notably, studies on LDL receptor and apolipoprotein E knockout mice provided support to the concept that circulating lipoproteins prevent or attenuate the consequences of sepsis through binding to or neutralising bacterial toxins such as lipopolysaccharides of Gram-negative bacteria.^{10,11} In agreement with these findings, hypolipidaemic mice models compared with the wild-type controls with normal lipid levels showed an increase in lipopolysaccharide-induced mortality.¹² Consequently, several clinical studies examined the association between LDL-C levels



and mortality from diverse infections and sepsis and the results were contradictory. A series of studies suggested that HLP reduces the risk of incident infection^{13 14} and sepsis^{13 15} and promotes favourable clinical outcome after certain infective conditions.^{16 17} Conversely, lower LDL-C concentration was associated with increased incidence of community-acquired sepsis,^{14 15 18} increased rates of death from pneumonia¹⁷ and poor clinical outcomes in patients with sepsis.^{14 15} Although the data from these observational studies may suggest a direct effect of LDL-C on incident sepsis and its outcome, unmeasured confounders might be of concern for biased effect. Accordingly, a large observational study found that low LDL-C level was associated with increased risk of sepsis and sepsis-related intensive care unit hospitalisation when the data were unadjusted, but no significant association when analyses were accounted for demographics and several comorbidities.¹⁹ Contradicting these observations, several other reports alluded that low level of LDL-C not only predicts increased risk of incident sepsis but is also associated with poor clinical outcome after diverse infectious conditions, even when adjusted for known confounders.^{14 15 17 18}

It is important to clearly understand the association between HLP and acute infective conditions because current guidelines recommend reduction of LDL-C concentration to much lower levels for secondary prophylaxis against cardiovascular events.²⁰

The primary objective of the present study was to assess both short-term and long-term risk of death from any cause among hospitalised patients with pneumonia who had concurrent HLP compared with those with no HLP. The secondary objective was to seek the direct association between LDL-C level and mortality to overcome provider-bias in documenting HLP as a secondary diagnosis on admission. To perceive this we collected data on LDL-C clinically measured within the preceding 180 days of admission. We used both initial unmatched cohort and propensity score matched groups to define how demographics, clinical characteristics and year of hospitalisation impact the association between HLP and mortality from pneumonia.

METHODS

Study population and data collection

The study cohort comprised of consecutive adults aged ≥18 years hospitalised at Mayo Clinic from 1 August 1996 to 17 September 2015 with primary discharge diagnosis of pneumonia. Discharge diagnoses were identified by the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes (480.0, 481.0, 482.0, 483.0, 484.0, 485.0, 486.0 and 487.0). These diagnostic codes have high positive predictive value for identification of pneumonia.²¹ Demographics, clinical characteristics, 20 US Department of Health and Human Services designated comorbidities, LDL-C levels, statin use and mortality data were all extracted from the Mayo Clinic inpatient database by professional data abstractionists.

Further details of data extraction are published elsewhere.²² We excluded patients who refused participation in clinical trials and those outside the Mayo Clinic catchment areas. Mayo Clinic has one of the oldest and most advanced medical record systems in the USA and its electronic medical records provide comprehensive information on patient characteristics. Patient-provided information is constantly updated at every clinic or hospital visit at its main Rochester campus and at the network of clinics and hospitals across more than 60 communities in the states of Iowa, Minnesota and Wisconsin.

Ascertainment of comorbid conditions

We focused on a panel of 20 comorbid conditions (CCs) defined by the Department of Health and Human Services²³ identified by Clinical Classifications Software codes developed by the US Healthcare Cost Utilization Project. These CCs are among the most common long-term conditions and most likely to persist indefinitely. CCs with prevalence <3% were excluded from analysis.

Ascertainment of HLP and statin use

Details about ascertainment of HLP have been described in our previous publications.^{24 25} In brief, HLP was defined as provider-documented pre-existing diagnosis or a new in-hospital diagnosis based on LDL-C level ≥100 mg/dL during index hospitalisation or within the preceding 6 months. Similarly, the diagnosis of 'no hyperlipidaemia' was assigned to those with no provider documentation of pre-existing HLP on admission. Patients with pre-existing diagnosis of no HLP were reclassified as hyperlipidaemic based on available LDL-C. The physician-reported diagnosis of HLP at baseline was presumably based on then clinical practice in accordance with the National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III).²⁶ Although we relied mainly on physician-reported diagnosis of HLP with potential provider-reported bias, cardiovascular comorbidities are generally considered as most reliably coded conditions in administrative data.²⁷ LDL-C was measured indirectly by the Friedewald method.²⁸ Published reports confirmed that lipid panel measured during the first 24 hours after an acute cardiovascular event reliably represents baseline level.²⁹ Statin use was evaluated based on medication reconciliation at the time of discharge.

Ascertainment of mortality

All deaths occurring from admission to the end of the study period, 17 August 2017, were abstracted. Mortality data at Mayo Clinic were constantly updated in patients' electronic medical records by primary care providers across the main campus and its network of clinics and hospitals. At the time of data analysis, Minnesota all-cause electronic death certificate data were current to 31 December 2018.

Statistical analysis

All statistical analyses were performed using SAS V.9.4. The significance threshold was a two-tailed p value of ≤ 0.05 for all statistical tests. Descriptive statistics were summarised as mean, SD, median and IQR for continuous variables and frequencies with percentages for categorical variables.

Propensity score analysis

We assembled propensity score matched pairs of patients with pneumonia to minimise the imbalance from measured baseline covariates between patients with concurrent HLP and those with no HLP. The matched groups were balanced for age, gender, ethnicity, length of hospital stay (LOS), comorbidities (coronary artery disease (CAD), cancer, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), diabetes, heart failure, hypertension and stroke), statin prescription on discharge and year of hospitalisation (table 1). Propensity scores were estimated using logistic regression (PROC PSMATCH in SAS V.9.4). One-to-one nearest neighbour calliper matching was used to match patients based on the propensity score using a calliper equal to 0.2 of the SD of the logit of the propensity score. Each patient in the study groups (HLP vs no HLP) has the same propensity to be allocated to either group. Standardised difference for each baseline characteristic was estimated to examine potential imbalance between HLP and no HLP groups. The absolute standardised difference was measured as a ratio of group means and the pooled SD.³⁰

Kaplan-Meier estimates

Kaplan-Meier estimates were performed in both unmatched and matched cohorts, and stratified log-rank tests were used to compare cumulative incidence of death at 28 days and in the longer term following hospitalisation for pneumonia. Separate Kaplan-Meier curves were generated for patients with available LDL-C data.

Multivariable Cox models

Cox proportional hazards models were performed to estimate HR and 95% CI for all-cause mortality. In propensity score matched cohorts, Cox regression models were performed with robust variance estimator to account for matching.

Subgroup analysis

We examined the association between quartiles of LDC-C and all-cause mortality in patients with pneumonia who had LDL-C cholesterol levels measured (as clinically indicated) on or within the preceding 180 days of index admission.

Patient and public involvement

Patients and the public were not involved in the design, conduct or reporting of this retrospective cohort study.

RESULTS

Baseline characteristics

Unmatched cohort

Figure 1 illustrates the Strengthening the Reporting of Observational Studies in Epidemiology flow diagram for selection of final study cohorts. The baseline characteristics of the study cohorts are presented in table 1 for both the initial unmatched cohort and the propensity score matched cohort, stratified by the presence or absence of concurrent HLP. The final unmatched cohort consisted of 8553 adults with a mean age 68.9 years (SD 17.2), 4509 (53%) men and 7506 (88%) whites. The aetiologies of pneumonia were as follows: unspecified organisms (n=6831, 80%), *Streptococcus pneumoniae* and other *Streptococcus* species (n=425, 5%), methicillin-susceptible *Staphylococcus aureus* (n=170, 2%), methicillin-resistant *Staphylococcus aureus* (n=50, 0.6%), *Legionella* (n=42, 0.5%), *Pseudomonas* (n=163, 2%), other Gram-negative bacteria (n=85, 1%), other specified bacteria (n=111, 1%), other unspecified bacteria (n=203, 2%), influenza and parainfluenza (n=214, 2%), respiratory syncytial virus (n=61, 0.7%) and other viruses (n=52, 0.6%). Compared with patients with pneumonia with no HLP, those with concurrent HLP were older, more often non-Hispanic whites and more likely to be prescribed statins on discharge. In the overall unmatched cohort, patients with HLP were more likely than those with no HLP to have their LDL-C measured during or within 6 months of hospitalisation (77% vs 38%), essentially representing a clinical practice of close laboratory follow-up of patients with pre-existing HLP. With the exception of stroke, patients with HLP more frequently have had other major comorbidities including hypertension, CAD, diabetes mellitus, CKD, heart failure or cancer than those with no HLP. Of the entire study population, 2334 (27%) patients had a concurrent diagnosis of HLP on admission. Of 20 CCs examined, only 8 were included in the final data analysis for their frequency $\geq 3\%$.

Propensity score matched groups

Propensity score matching resulted in 1879 pairs of patients with and with no HLP. As shown in table 1, the imbalance in measured baseline characteristics was minimised in propensity score matched groups compared with the unmatched cohort, with absolute standardised difference < 0.1 for most covariates. However, residual imbalance persisted for LOS, heart failure and statin therapy.

Mortality

Adjusted HRs for mortality at 28 days and at a median follow-up of 3.9 years are presented in table 2.

Unmatched cohort

In the unmatched cohort, 588 patients (6.9%) died within 28 days after index hospitalisation for pneumonia. The overall mortality was 5209 over 47839 person-years

Table 1 Baseline patient characteristics and absolute standardised difference before and after 1:1 propensity score matching of patients with pneumonia with or without concurrent hyperlipidaemia

Study groups	Pneumonia, unmatched entire cohort, n=8553			Pneumonia, matched entire cohort, n=3764		
	With hyperlipidaemia n=2278 (27%)	With no hyperlipidaemia n=6275 (73%)	P value	With hyperlipidaemia n=1879	With no hyperlipidaemia n=1879	P value
Demographics						
Overall age, years, mean±SD	71.1±14.1	68.0±18.0	<0.0001	70.5±14.5	64.2±18.5	<0.0001
Age <65, n (%)	680 (29)	2296 (37)	<0.0001	574 (31)	904 (48)	
Age ≥65, n (%)	1654 (71)	3923 (63)		1306 (69)	978 (52)	
Male, n (%)	1250 (54)	3259 (52)	0.9040	997 (53)	997 (53)	1.000
Female, n (%)	1084 (46)	2960 (48)		885 (47)	885 (47)	1.000
White, n (%)	2159 (93)	5344 (86)	<0.0001	1734 (92)	1734 (92)	1.000
Non-white, n (%)	175 (7)	875 (14)		148 (8)	148 (8)	1.000
Anthropometric measurements						
BMI, kg/m ²	29.6±7.3	27.9±7.3	<0.0001	29.2±7.1	28.9±7.9	0.3165
BMI, missing, n (%)	36 (2.0)	964 (14.0)		0	0	
Clinical characteristics						
LOS, days, median (quartiles 25%–75%)	3 (2–5)	3 (2–6)	<0.0001	3 (2–5)	4 (2–7)	<0.0001
Comorbid conditions with prevalence ≥3%						
CAD, n (%)	706 (42)	983 (14)	<0.0001	612 (32)	319 (17)	<0.0001
Cancer, n (%)	501 (29)	1595 (23)	0.0044	486 (26)	459 (24)	0.3284
CKD, n (%)	386 (28)	668 (10)	<0.0001	312 (16)	310 (16)	0.9650
COPD, n (%)	497 (29)	1795 (26)	0.1615	507 (27)	438 (23)	0.0106
Diabetes, n (%)	608 (36)	1204 (18)	<0.0001	524 (28)	585 (31)	0.0319
Heart failure, n (%)	330 (20)	1082 (16)	0.0053	321 (17)	291 (15)	0.2002
Hypertension, n (%)	1277 (75)	2775 (40)	<0.0001	1115 (59)	990 (53)	<0.0001
Stroke, n (%)	54 (3)	92 (13)	<0.0001	46 (2)	54 (3)	0.4782
Lipid levels						
LDL-C, mg/dL	87.9±38.0	97.9±38.5	<0.0001	109.0±40.5	87.0±36.0	<0.0001
LDL-C, missing data, n (%)	541 (31.9)	3885 (56.6)		447 (24)	1019 (54)	
Drug treatment						
Statin	1133 (49)	1033 (17)	<0.0001	683 (36)	610 (32)	0.0134
Follow-up						
Median (quartiles 25%–75%), years	4.0 (1.5–7.4)	3.9 (1.0–9.4)	0.5103	4.1 (1.5–8.3)	4.5 (1.5–8.8)	0.0875
Person-years	11 910	35 914		10 128	10 979	

BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; LDL-C, low-density lipoprotein cholesterol; LOS, length of hospital stay.

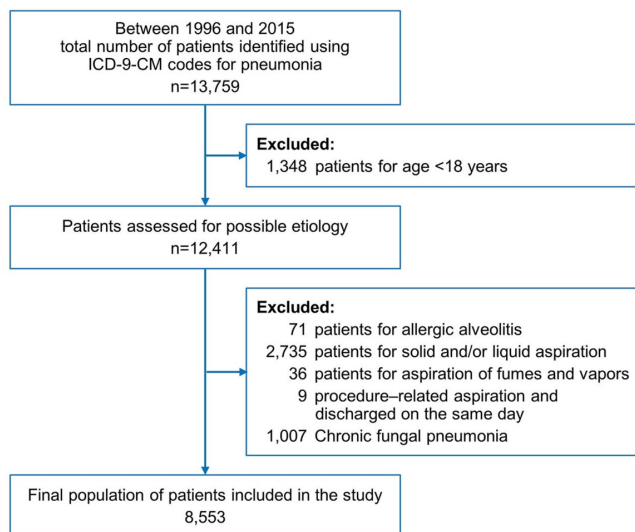


Figure 1 Strengthening the Reporting of Observational Studies in Epidemiology flow diagram of selection of the final study cohort. ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.

or over a median follow-up of 3.9 years (IQR 1.2–8.8 years). Cumulative all-cause mortality was significantly lower in patients with HLP compared with those with no HLP at 28 days (HLP 91/2334 (3.9%) vs 497/6219 (8%), log-rank $p < 0.0001$) or at 4-year median follow-up (HLP 1258/2334 (54%); no HLP 3951/6219 (64%), $p < 0.0001$).

Propensity score matched groups

Mortality difference between HLP and no HLP was maintained among propensity score matched groups. Overall 2146 patients died over 19671 person-years of follow-up (median 4 years; IQR 1.3–8.1 years), including 217 patients (5.8%) who died within 28 days of hospitalisation. Cumulative all-cause mortality was significantly lower in patients with HLP compared with those with no HLP both at 28 days (HLP 83/1879 (4.4%) vs 134/1879 (7.1%), log-rank $p < 0.0004$) or at 4-year median follow-up (HLP 1036/1879 (55%); no HLP 1110/1879 (59%), $p = 0.0106$).

Kaplan-Meier estimates

Unmatched cohort

Figures 2A and 3A display the Kaplan-Meier estimates of cumulative incidence of death at 28 days and in the longer term (range 0–20 years), respectively, in patients with pneumonia stratified by the presence or absence of HLP. Kaplan-Meier mortality curves separated soon after hospitalisation and remained parallel until 12 years, when curves converged and remained so during the remaining of the follow-up period. The median time to death was 6.3 years (95% CI 5.8 to 6.9) and 5.1 years (95% CI 4.7 to 5.4) among patients with HLP and no HLP, respectively, without overlap in 95% CI. In secondary analysis of patients who had data on clinically measured LDL-C, a

mortality gradient was found, with the lowest mortality in patients with LDL-C ≥ 130 mg/dL and highest mortality among patients with LDL-C ≤ 70 mg/dL (figure 3B).

Propensity score matched groups

Risk difference in mortality between HLP and no HLP both at 28 days and in the longer term was similar to those in the unmatched cohort. Kaplan-Meier mortality curves diverged soon after hospitalisation and remained parallel until 10 years into follow-up when they began converging (28-day mortality in figure 2B; long-term mortality in figure 3C). The median time to death was 6.5 years (95% CI 6.0 to 7.3) and 5.2 years (95% CI 4.7 to 5.8) among patients with HLP and no HLP, respectively, without overlap in 95% CI. Similar to secondary analysis data in the unmatched cohort, mortality gradient across LDL-C quartiles was maintained across propensity score matched groups (figure 3D).

Cox proportional regression models

Unmatched cohort

The multivariable Cox model estimated that the hazard of death from any condition was 48% lower at 28 days (HR 0.52, 95% CI 0.41 to 0.66, $p < 0.0001$) and 25% lower in the longer term (HR 0.75, 95% CI 0.70 to 0.80) in patients who had concurrent HLP compared with those who did not. The risk difference in all-cause mortality between patients with HLP and those with no HLP was independent of age, gender, ethnicity, LOS, concurrent eight CCs and use of statin therapy. Except for hypertension and CAD, all other CCs were identified as independent predictors of increased mortality. In a subgroup of 4126 patients who had LDL-C data available, multivariable Cox model estimated that hazard of death from any condition was 33% lower (HR 0.67, 95% CI 0.59 to 0.77, $p < 0.0001$) in patients with the highest LDL-C quartile (LDL-C ≥ 130 mg/dL) compared with those with the lowest LDL-C quartile (LDL-C < 70 mg/dL) (table 2).

Propensity score matched groups

The multivariable Cox model with robust variance estimator to account for matching estimated that the hazard of death from any condition was 35% lower at 28 days (HR 0.65, 95% CI 0.49 to 0.86, $p = 0.0013$) and 12% lower in the longer term (HR 0.88, 95% CI 0.81 to 0.96, $p = 0.0030$) in patients who had concurrent HLP compared with those who did not. The risk difference in mortality was consistent across the following subgroups: male (HR 0.86, 95% CI 0.75 to 0.96, $p = 0.0101$), female (HR 0.91, 95% CI 0.80 to 1.03, $p = 0.1330$), white (HR 0.91, 95% CI 0.83 to 0.99, $p = 0.0304$) and non-white (HR 0.65, 95% CI 0.46 to 0.91, $p = 0.0127$). In a subgroup of 2306 patients who had LDL-C data available, multivariable Cox model estimated that the hazard of death from any condition was 20% lower (HR 0.80, 95% CI 0.68 to 0.97, $p = 0.0190$) in patients with the highest LDL-C quartile (LDL-C

Table 2 HR based on multivariable adjusted Cox regression analysis of the association of hyperlipidaemia and other covariates with all-cause mortality in unmatched and propensity score matched patients with pneumonia

Covariates	Unmatched cohort, n=8553		Propensity score matched cohort, n=1879	
	HR (95% CI)	P value	HR (95% CI)	P value
Long-term mortality, median follow-up 3.9 years				
Age	1.04 (1.03 to 1.04)	<0.0001	1.04 (1.04 to 1.05)	<0.0001
Male vs female	1.14 (1.07 to 1.20)	<0.0001	1.12 (1.02 to 1.22)	0.0135
White vs non-white	0.90 (0.83 to 0.98)	0.0176	0.90 (0.76 to 1.06)	0.1970
Length of stay	1.02 (1.01 to 1.02)	<0.0001	1.03 (1.03 to 1.04)	<0.0001
Cancer vs no cancer	1.98 (1.86 to 2.01)	<0.0001	1.80 (1.64 to 1.98)	<0.0001
CKD vs no CKD	1.26 (1.16 to 1.37)	<0.0001	1.36 (1.22 to 1.53)	<0.0001
COPD vs no COPD	1.23 (1.16 to 1.30)	<0.0001	1.20 (1.10 to 1.32)	<0.0001
DM vs no DM	1.10 (1.03 to 1.18)	0.0040	1.16 (1.05 to 1.27)	0.0022
HLP vs no HLP	0.75 (0.70 to 0.80)	<0.0001	0.88 (0.81 to 0.96)	0.0030
HF vs no HF	1.30 (1.21 to 1.40)	<0.0001	1.29 (1.16 to 1.43)	<0.0001
CAD	1.02 (0.95 to 1.09)	0.5572	1.06 (0.97 to 1.17)	0.1991
HTN	0.97 (0.91 to 1.02)	0.3305	0.99 (0.90 to 1.09)	0.8598
Stroke vs no stroke	1.25 (1.04 to 1.52)	0.0193	1.35 (1.06 to 1.72)	0.0135
28-day mortality from date of hospitalisation				
Age	1.03 (1.03 to 1.04)	<0.0001	1.03 (1.02 to 1.04)	<0.0001
Male vs female	1.18 (0.99 to 1.40)	0.0517	0.92 (0.70 to 1.22)	0.5776
White vs non-white	0.53 (0.44 to 0.66)	<0.0001	0.49 (0.32 to 0.74)	0.0008
Length of stay	1.03 (1.02 to 1.03)	<0.0001	1.05 (1.03 to 1.07)	<0.0001
Cancer vs no cancer	2.35 (1.98 to 2.79)	<0.0001	2.29 (1.73 to 3.03)	<0.0001
CKD vs no CKD	0.92 (0.70 to 1.20)	0.5355	1.06 (0.74 to 1.52)	0.7387
COPD vs no COPD	0.88 (0.73 to 1.06)	0.1871	0.89 (0.66 to 1.21)	0.4574
DM vs no DM	0.92 (0.74 to 1.14)	0.4602	0.78 (0.57 to 1.08)	0.1336
HLP vs no HLP	0.52 (0.41 to 0.66)	<0.0001	0.65 (0.49 to 0.86)	0.0025
HF vs no HF	1.72 (1.41 to 2.08)	<0.0001	1.65 (1.22 to 2.23)	0.0013
CAD	0.91 (0.73 to 1.13)	0.3926	1.05 (0.78 to 1.42)	0.7438
HTN	0.74 (0.62 to 0.88)	0.0009	0.73 (0.55 to 0.97)	0.0289
Stroke vs no stroke	1.96 (1.23 to 3.11)	0.0043	1.10 (0.51 to 2.34)	0.8086

Cox regression model was adjusted for age, sex, race, length of hospital stay and key comorbid conditions including cancer, CKD, CAD, COPD, DM, HF, HTN, stroke and HLP.

A robust variance estimator to account for matching was used to estimate HR in matched cohort.

CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HF, heart failure; HLP, hyperlipidaemia; HTN, hypertension.

≥130 mg/dL) compared with those with lowest LDL-C quartile (LDL-C <70 mg/dL).

Subgroup definitions and analysis

To examine the effect of age on the association between HLP and long-term all-cause mortality, we constructed separate Kaplan-Meier mortality estimates and conducted multivariable Cox regression analysis across age groups: <65 years and ≥65 years. The results are presented in online supplemental figure 1A,B. HLP significantly lowered all-cause mortality following pneumonia in patients aged ≥65 years (log-rank $p<0.0001$; adjusted HR 0.84, 95% CI 0.76 to 0.93, $p=0.0005$) but not in those aged <65 years (log-rank $p=0.6889$, adjusted HR 0.85,

95% CI 0.69 to 1.03, $p=0.0965$). To assess the impact of cardiometabolic comorbidities with or with no HLP on postpneumonia mortality, we adopted a scheme reported in our previous study.³¹ Cardiometabolic comorbidity with pneumonia was defined as concurrent diabetes mellitus, CAD or heart failure. Overall 2080 (55%) had one or other concurrent cardiometabolic conditions in association with pneumonia. The presence of any of the three cardiometabolic conditions significantly increased all-cause mortality after hospitalisation for pneumonia, as shown in online supplemental figure 2A) (log-rank $p<0.0001$, adjusted HR 1.36, 95% CI 1.24 to 1.49, $p<0.0001$). To determine the extent of HLP effect on the association between cardiometabolic comorbidity and

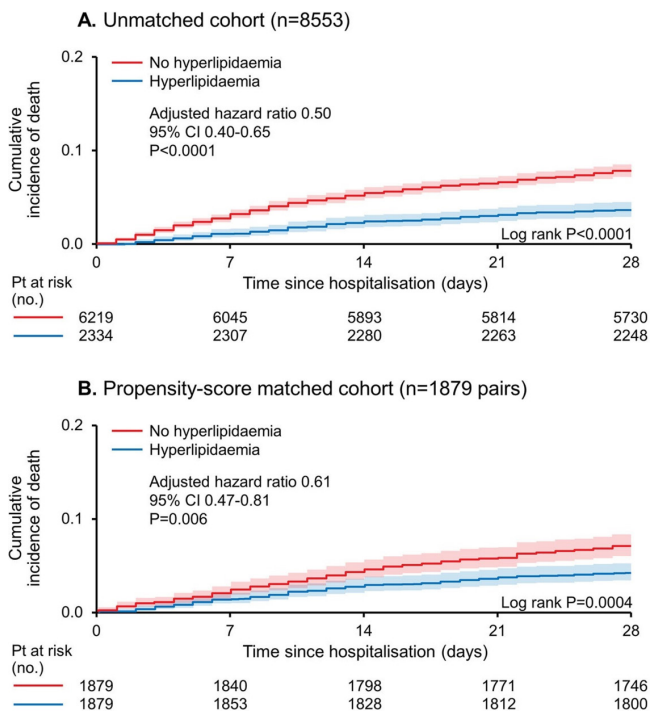


Figure 2 (A) Unmatched cohort (n=8553) and (B) propensity score matched cohort (n=1879 pairs).

all-cause mortality, we conducted parallel analysis again using Kaplan-Meier survival estimates Cox regression models. We found that the joint effect of HLP with cardiometabolic comorbidity was the attenuation of mortality difference, as presented in online supplemental figure 2B (log-rank $p<0.0001$, adjusted HR 1.05, 95% CI 0.95 to 1.16, $p=0.2915$).

Sensitivity analysis

Sensitivity analyses were performed by excluding (1) patients with no available data on body mass index and (2) patients with no available data on prescription statin on dismissal. The association between HLP and mortality among patients with pneumonia remained similar.

DISCUSSION

Main findings

In this large, single-centre cohort of patients hospitalised for pneumonia, we found that a concurrent diagnosis of HLP compared with no HLP was associated with lower all-cause mortality in the overall population and in the propensity score matched groups at both shorter-term (28 days) and longer-term (median 4 years) follow-up. First, HLP as a concurrent diagnosis among hospitalised patients with pneumonia predicted 10% fewer deaths at a median follow-up of 3.9 years in the entire population and 4% fewer deaths in propensity score matched groups at a median follow-up of 4 years. Second, concordant with the primary findings, LDL-C quartiles showed graded inverse associations with all-cause mortality both in the entire unmatched cohort and in propensity score matched groups mitigating provider bias for

the diagnosis of HLP. Furthermore the associations between, age, gender, ethnicity, LOS, CAD, cancer, CKD, COPD, diabetes, heart failure, hypertension, stroke or statin therapy and all-cause mortality were comparable among unmatched population of patients and matched groups. Third, our findings were also noticeable for lower frequency of documented bacterial and viral infections as the cause of pneumonia and the aetiology remained unknown in 80% of patients based on their diagnostic tests, a finding broadly similar to a recent report from the US Centers for Disease Control³² and a meta-analysis showing a decline in the prevalence of pneumococcal infection especially in the USA.³³ Sociodemographic indicators of study population especially older age, lower frequency of cigarette smoking and substance use disorder compared with the US national average potentially account for these discrepant findings.

Comparative studies in the clinical context

Pneumonia is associated with excess long-term mortality compared with several other acute conditions requiring hospitalisation³⁴ and adversely impact survival far beyond initial hospitalisation.³⁵⁻³⁷ Patients surviving initial hospitalisation for pneumonia are at increased risk for subsequent hospitalisations and mortality as high as 50% within 5 years of index hospitalisation.³⁸ In our previous report on the risk of comorbidities on long-term mortality after hospitalisation for pneumonia, we discussed that pneumonia is associated with excess mortality and adversely impact survival far beyond the initial hospitalisation.³⁹ It is unclear why and how elevated cholesterol is potentially beneficial for all-cause mortality following hospitalisation for pneumonia. The association between HLP and infection-related mortality is even less clearly understood and is an area of great interest. Published data on the association of HLP and mortality from pneumonia are limited, and we therefore sought insights from studies in cardiovascular and other infectious conditions to give credence to our findings.

The relationship between HLP and acute myocardial infarction or heart failure had been extensively investigated; however, the data remain inconclusive specifically for patients with established acute myocardial infarction and heart failure. Whereas randomised clinical trials especially those focused on lowering LDL-C by statins and more recently proprotein convertase subtilisin/kexin type 9 inhibitors provide compelling evidence for survival benefit with lowering LDL-C cholesterol, several other studies found an inverse association where HLP counterintuitively conferred an overall survival benefit in patients with established acute myocardial infarction⁴⁰⁻⁴³ and heart failure.⁴⁴ In propensity score matched cohort studies and systematic review and meta-analysis, we reported a survival benefit with HLP after hospitalisation for acute myocardial infarction and heart failure.^{24 25} In an analysis of initial and subsequent 3-year cost after hospitalisation for first-ever ischaemic stroke, we also reported that HLP predicts a lower 3-year cost mainly through a reduction in rates of readmission after index hospitalisation.⁴⁵

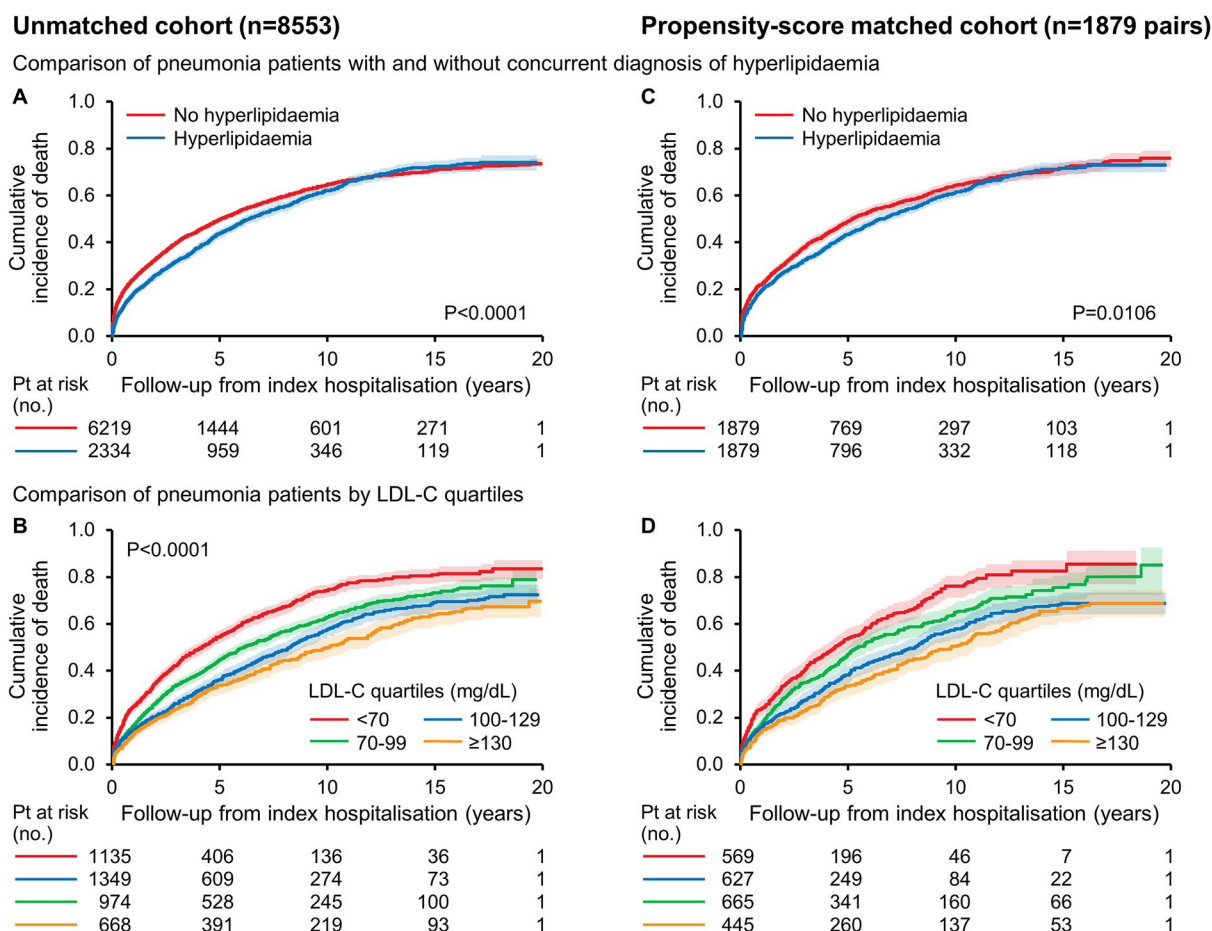


Figure 3 Kaplan-Meier mortality estimates comparing pneumonia patients with and with no concurrent hyperlipidaemia and by low density lipoprotein cholesterol (LDL-C) quartiles. A) unmatched original cohort patients with and with no hyperlipidaemia, B) unmatched original cohort patients by LDL-C quartiles, C) propensity-score matched cohort patients with and with no hyperlipidaemia, D) propensity-score matched cohort patients by LDL-C quartiles.

A number of epidemiological studies demonstrated that low cholesterol increases the risk of infection,^{14 46} and our findings in the present study provide evidence that the effects of elevated cholesterol extend far beyond acute care hospitalisation for pneumonia and predict a lower risk of death both at short-term and longer-term follow-up. Several studies that have examined the relationship between HLP and sepsis reported widely variable results. Published studies that examined the relationship between HLP and outcome from infections have largely focused on widely different infectious conditions. Two studies specifically examined the relationship between HLP and incident pneumonia and ensuing mortality.^{13 17} In these studies HLP was associated with reduced incident pneumonia and mortality.^{13 17} Similar to our findings in patients with pneumonia, the association between low cholesterol concentration and increased mortality from infections has been reported for patients with end-stage renal disease undergoing dialysis.⁴⁶⁻⁴⁹ Likewise, lower serum cholesterol concentration was independently associated with increased mortality among patients with heart failure,⁵⁰ cancer⁵¹ and AIDS.⁵² Current findings in pneumonia together with our previous studies focused on patients with acute myocardial infarction and heart failure

provide persuasive evidence for a more favourable effect of HLP, compared with no HLP, on long-term clinical outcomes in diverse clinical conditions.^{24 25}

Several studies suggested that statins reduce mortality among patients with sepsis presumably through their anti-inflammatory and immune modulatory effects. Over the past 15 years, several prospective cohort studies and randomised controlled clinical trials examined the effect of cholesterol-lowering by statins on mortality among patients with sepsis.^{53 54} The results of several meta-analyses of these clinical studies were inconclusive.⁵⁵⁻⁶¹ Nevertheless, a recent meta-analysis of seven randomised clinical trials showed no benefit of statin therapy on mortality in patients with sepsis compared with placebo.⁶² Our findings, on the other hand, demonstrated a clear mortality benefit with statin therapy independent of other covariates and warrant further studies to validate these results.

Strengths and limitations

This study has several strengths. The large study cohorts and the high level of case ascertainment for incident events and prompt mortality update⁶³ allowed precise estimation

of mortality risks. Other important strengths are the broad range of patient population and follow-up extending to 20 years. Propensity score matching to balance observed patient characteristics enabled further control of potential differences. The study also has a number of important limitations as follows: inherent limitations of a retrospective observational design, the possibility of unmeasured confounders, reliance on ICD-9-CM codes to identify study cohort, Clinical Classifications Software codes to assess coexisting CCs, ascertainment of CCs during index hospitalisation and lack of data on subsequent acquisition of these conditions during the follow-up. Our study cohorts were homogenous with respect to race and substantially older than those observed in most clinical trials, but similar to those in many epidemiological studies. The proportion of patients with no LDL-C data was higher in the group with no HLP potentially due to less frequent measurement of lipid levels in persons with no HLP and may constitute an important unmeasured confounder since propensity score matching was not accounted for this variable. The pre-existing HLP and CCs were physician-diagnosed during index hospitalisation rather than being assigned by study investigators. To overcome physician bias for the diagnosis of HLP or no HLP, we examined direct association between LDL-C and mortality among subgroup of patients who had their cholesterol levels measured on admission or within the preceding 6 months and the results were consistent. Our analysis demonstrated that the proportion of patients with no LDL data was higher among patients with no HLP.

CONCLUSIONS

In this large, retrospective, single-centre study of real-world hospitalised patients with pneumonia, a concurrent diagnosis of HLP in hospitalised patients with pneumonia was protective on the subsequent short-term and long-term death after adjustment for other major contributors to mortality in both unmatched and propensity score matched cohorts. We sought the direct association between LDL-C levels, stratified by quartiles, and mortality to overcome provider bias in documenting HLP as a secondary diagnosis on admission and demonstrated that LDL-C quartiles were inversely related to mortality. Importantly, these associations between HLP or LDL-C quartiles were maintained after adjustments for several measured covariates in propensity score matched groups. Although our data are convincing, further research is needed to validate our findings in large unselect populations and diverse clinical conditions.

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REFERENCES

- 1 Yusuf S, Hawken S, Ounpuu S, *et al*. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004;364:937–52.
- 2 LaRosa JC, Hunninghake D, Bush D, *et al*. The cholesterol facts. A summary of the evidence relating dietary fats, serum cholesterol, and coronary heart disease. A joint statement by the American heart association and the National heart, lung, and blood Institute. The task force on cholesterol issues, American heart association. *Circulation* 1990;81:1721–33.
- 3 Stamler J, Wentworth D, Neaton JD. Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? findings in 356,222 primary screenees of the multiple risk factor intervention trial (MRFIT). *JAMA* 1986;256:2823–8.
- 4 Baigent C, Blackwell L, *et al*. Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 2010;376:1670–81.
- 5 Mihaylova B, Emberson J, Cholesterol Treatment Trialists' (CTT) Collaborators, *et al*. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet* 2012;380:581–90.
- 6 Lewington S, Whitlock G, Prospective Studies Collaboration, *et al*. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. *Lancet* 2007;370:1829–39.
- 7 Silverman MG, Ference BA, Im K, *et al*. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: a systematic review and meta-analysis. *JAMA* 2016;316:1289–97.
- 8 Feingold KR, Grunfeld C. Lipoproteins: are they important components of host defense? *Hepatology* 1997;26:1685–6.
- 9 Rauchhaus M, Coats AJ, Anker SD. The endotoxin-lipoprotein hypothesis. *Lancet* 2000;356:930–3.
- 10 de Bont N, Netea MG, Demacker PN, *et al*. Apolipoprotein E knockout mice are highly susceptible to endotoxemia and Klebsiella pneumoniae infection. *J Lipid Res* 1999;40:680–5.
- 11 Netea MG, Demacker PN, Kullberg BJ, *et al*. Low-Density lipoprotein receptor-deficient mice are protected against lethal endotoxemia and severe gram-negative infections. *J Clin Invest* 1996;97:1366–72.
- 12 Feingold KR, Funk JL, Moser AH, *et al*. Role for circulating lipoproteins in protection from endotoxin toxicity. *Infect Immun* 1995;63:2041–6.
- 13 Chan M-C, Lin C-H, Kou YR. Hyperlipidemia in COPD is associated with decreased incidence of pneumonia and mortality: a nationwide health insurance data-based retrospective cohort study. *Int J Chron Obstruct Pulmon Dis* 2016;11:1053–9.
- 14 Guirgis FW, Donnelly JP, Dodani S, *et al*. Cholesterol levels and long-term rates of community-acquired sepsis. *Crit Care* 2016;20:408.
- 15 Lagrost L, Girard C, Grosjean S, *et al*. Low preoperative cholesterol level is a risk factor of sepsis and poor clinical outcome in patients undergoing cardiac surgery with cardiopulmonary bypass. *Crit Care Med* 2014;42:1065–73.
- 16 Chien J-Y, Jerng J-S, Yu C-J, *et al*. Low serum level of high-density lipoprotein cholesterol is a poor prognostic factor for severe sepsis. *Crit Care Med* 2005;33:1688–93.



- 17 Chien Y-F, Chen C-Y, Hsu C-L, *et al.* Decreased serum level of lipoprotein cholesterol is a poor prognostic factor for patients with severe community-acquired pneumonia that required intensive care unit admission. *J Crit Care* 2015;30:506–10.
- 18 Shor R, Wainstein J, Oz D, *et al.* Low serum LDL cholesterol levels and the risk of fever, sepsis, and malignancy. *Ann Clin Lab Sci* 2007;37:343–8.
- 19 Feng Q, Wei W-Q, Chaugai S, *et al.* Association between low-density lipoprotein cholesterol levels and risk for sepsis among patients admitted to the hospital with infection. *JAMA Netw Open* 2019;2:e187223.
- 20 Grundy SM, Stone NJ, Bailey AL. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APHA/ASPC/NLA/PCNA guideline on the management of blood cholesterol. *Circulation*;2018.CIR0000000000000625.
- 21 Drahos J, Vanwormer JJ, Greenlee RT, *et al.* Accuracy of ICD-9-CM codes in identifying infections of pneumonia and herpes simplex virus in administrative data. *Ann Epidemiol* 2013;23:291–3.
- 22 Yousufuddin M, Bartley AC, Alsawas M, *et al.* Impact of multiple chronic conditions in patients hospitalized with stroke and transient ischemic attack. *J Stroke Cerebrovasc Dis* 2017;26:1239–48.
- 23 Goodman RA, Posner SF, Huang ES, *et al.* Defining and measuring chronic conditions: imperatives for research, policy, program, and practice. *Prev Chronic Dis* 2013;10:E66.
- 24 Yousufuddin M, Takahashi PY, Major B, *et al.* Association between hyperlipidemia and mortality after incident acute myocardial infarction or acute decompensated heart failure: a propensity score matched cohort study and a meta-analysis. *BMJ Open* 2019;9:e028638.
- 25 Yousufuddin M, Zhu Y, Al Ward R, *et al.* Association of hyperlipidaemia with 5-year survival after hospitalisation for acute myocardial infarction: a propensity score matched analysis. *Open Heart* 2020;7:e001163.
- 26 Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). *JAMA* 2001;285:2486–97.
- 27 Hua-Gen Li M, Hutchinson A, Tacey M, *et al.* Reliability of comorbidity scores derived from administrative data in the tertiary hospital intensive care setting: a cross-sectional study. *BMJ Health Care Inform* 2019;26:e000016.
- 28 Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972;18:499–502.
- 29 Pitt B, Loscalzo J, Ycas J, *et al.* Lipid levels after acute coronary syndromes. *J Am Coll Cardiol* 2008;51:1440–5.
- 30 Heinze G, Jüni P. An overview of the objectives of and the approaches to propensity score analyses. *Eur Heart J* 2011;32:1704–8.
- 31 Yousufuddin M, Young N, Keenan L, *et al.* Five-Year mortality after transient ischemic attack: focus on cardiometabolic comorbidity and hospital readmission. *Stroke* 2018;49:730–733.
- 32 Jain S, Self WH, Wunderink RG, *et al.* Community-Acquired pneumonia requiring hospitalization among U.S. adults. *N Engl J Med* 2015;373:415–27.
- 33 Musher DM, Abers MS, Bartlett JG. Evolving understanding of the causes of pneumonia in adults, with special attention to the role of pneumococcus. *Clin Infect Dis* 2017;65:1736–44.
- 34 Kaplan V, Angus DC, Griffin MF, *et al.* Hospitalized community-acquired pneumonia in the elderly: age- and sex-related patterns of care and outcome in the United States. *Am J Respir Crit Care Med* 2002;165:766–72.
- 35 Mortensen EM, Kapoor WN, Chang C-CH, *et al.* Assessment of mortality after long-term follow-up of patients with community-acquired pneumonia. *Clin Infect Dis* 2003;37:1617–24.
- 36 Mortensen EM, Metersky ML. Long-Term mortality after pneumonia. *Semin Respir Crit Care Med* 2012;33:319–24.
- 37 Sandvall B, Rueda AM, Musher DM. Long-Term survival following pneumococcal pneumonia. *Clin Infect Dis* 2013;56:1145–6.
- 38 Restrepo MI, Faverio P, Anzueto A. Long-Term prognosis in community-acquired pneumonia. *Curr Opin Infect Dis* 2013;26:151–8.
- 39 Yousufuddin M, Shultz J, Doyle T, *et al.* Incremental risk of long-term mortality with increased burden of comorbidity in hospitalized patients with pneumonia. *Eur J Intern Med* 2018;55:23–7.
- 40 Granger CB, Goldberg RJ, Dabbous O, *et al.* Predictors of hospital mortality in the global registry of acute coronary events. *Arch Intern Med* 2003;163:2345–53.
- 41 Krumholz HM, Seeman TE, Merrill SS, *et al.* Lack of association between cholesterol and coronary heart disease mortality and morbidity and all-cause mortality in persons older than 70 years. *JAMA* 1994;272:1335–40.
- 42 Reddy VS, Bui QT, Jacobs JR, *et al.* Relationship between serum low-density lipoprotein cholesterol and in-hospital mortality following acute myocardial infarction (the lipid paradox). *Am J Cardiol* 2015;115:557–62.
- 43 Wang TY, Newby LK, Chen AY, *et al.* Hypercholesterolemia paradox in relation to mortality in acute coronary syndrome. *Clin Cardiol* 2009;32:E22–8.
- 44 Kalantar-Zadeh K, Block G, Horwich T, *et al.* Reverse epidemiology of conventional cardiovascular risk factors in patients with chronic heart failure. *J Am Coll Cardiol* 2004;43:1439–44.
- 45 Yousufuddin M, Moriarty JP, Lackore KA, *et al.* Initial and subsequent 3-year cost after hospitalization for first acute ischemic stroke and intracerebral hemorrhage. *J Neurol Sci* 2020;419:117181.
- 46 Kaysen GA, Ye X, Raimann JG, *et al.* Lipid levels are inversely associated with infectious and all-cause mortality: international MONDO study results. *J Lipid Res* 2018;59:1519–28.
- 47 Avram MM, Mittman N, Bonomini L, *et al.* Markers for survival in dialysis: a seven-year prospective study. *Am J Kidney Dis* 1995;26:209–19.
- 48 Goldwasser P, Mittman N, Antignani A, *et al.* Predictors of mortality in hemodialysis patients. *J Am Soc Nephrol* 1993;3:1613–22.
- 49 Lowrie EG, Huang WH, Lew NL. Death risk predictors among peritoneal dialysis and hemodialysis patients: a preliminary comparison. *Am J Kidney Dis* 1995;26:220–8.
- 50 Rauchhaus M, Clark AL, Doehner W, *et al.* The relationship between cholesterol and survival in patients with chronic heart failure. *J Am Coll Cardiol* 2003;42:1933–40.
- 51 Chao FC, Efron B, Wolf P. The possible prognostic usefulness of assessing serum proteins and cholesterol in malignancy. *Cancer* 1975;35:1223–9.
- 52 Neaton JD, Wentworth DN. Low serum cholesterol and risk of death from AIDS. *AIDS* 1997;11:929–30.
- 53 Kruger P, Bailey M, Bellomo R, *et al.* A multicenter randomized trial of atorvastatin therapy in intensive care patients with severe sepsis. *Am J Respir Crit Care Med* 2013;187:743–50.
- 54 Patel JM, Snaith C, Thickett DR, *et al.* Randomized double-blind placebo-controlled trial of 40 mg/day of atorvastatin in reducing the severity of sepsis in ward patients (asepsis trial). *Crit Care* 2012;16:R231.
- 55 Cheng H-H, Tang T-T, He Q, *et al.* Beneficial effects of statins on outcomes in pneumonia: a systematic review and meta-analysis. *Eur Rev Med Pharmacol Sci* 2014;18:2294–305.
- 56 Deshpande A, Pasupuleti V, Rothberg MB. Statin therapy and mortality from sepsis: a meta-analysis of randomized trials. *Am J Med* 2015;128:410–7.
- 57 Jia M, Huang W, Li L, *et al.* Statins reduce mortality after Non-severe but not after severe pneumonia: a systematic review and meta-analysis. *J Pharm Pharm Sci* 2015;18:286–302.
- 58 Khan AR, Riaz M, Bin Abdulhak AA, *et al.* The role of statins in prevention and treatment of community acquired pneumonia: a systematic review and meta-analysis. *PLoS One* 2013;8:e52929.
- 59 Kwok CS, Yeong JK-Y, Turner RM, *et al.* Statins and associated risk of pneumonia: a systematic review and meta-analysis of observational studies. *Eur J Clin Pharmacol* 2012;68:747–55.
- 60 Thomas G, Hraiech S, Loundou A, *et al.* Statin therapy in critically-ill patients with severe sepsis: a review and meta-analysis of randomized clinical trials. *Minerva Anestesiol* 2015;81:921–30.
- 61 Tleyjeh IM, Kashour T, Hakim FA, *et al.* Statins for the prevention and treatment of infections: a systematic review and meta-analysis. *Arch Intern Med* 2009;169:1658–67.
- 62 Chen M, Ji M, Si X. The effects of statin therapy on mortality in patients with sepsis: a meta-analysis of randomized trials. *Medicine* 2018;97:e11578.
- 63 Whisnant JP, Melton LJ, Davis PH, *et al.* Comparison of case ascertainment by medical record linkage and cohort follow-up to determine incidence rates for transient ischemic attacks and stroke. *J Clin Epidemiol* 1990;43:791–7.