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ORIGINAL RESEARCH

Deaths from Acute Respiratory Infections are Linked to High Fasting Blood Glucose and Decreased Levels of Low-Density Lipoprotein/ Small Dense Low-Density Lipoprotein

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Purpose: Winter poses a significant threat to acute respiratory infections (ARIs), often leading to severe outcomes including mortality. This study investigated the effect of glucose and lipid metabolism on mortality rates among individuals with ARIs.

Patients and Methods: We collected clinical data including indicators related to glucose and lipid metabolism, liver and kidney function, complete blood count, coagulation function, and other parameters from 1675 hospitalized patients with ARIs who were consecutively admitted during the winter season. The clinical characteristics and influencing factors associated with mortality in these patients were analyzed.

Results: Risk factors contributing to mortality in patients with ARIs include fasting blood glucose (FBG), low-density lipoprotein (LDL), apolipoprotein E (ApoE), small dense LDL (sdLDL), D-dimer, lymphocyte count, blood urea nitrogen, and a history of diabetes. Notably, when FBG above 7.8 mmol/L, mortality followed a parabolic association with HbA1c-lowest at extremes (<5.7% or ≥8.5%) but markedly higher in the mid-range (5.7–8.4%). Among patients with diabetes, those who succumbed to the infection exhibited higher FBG levels but lower glycated hemoglobin (HbA1c) levels than those who recovered. Moreover, low levels of LDL/ sdLDL and high levels of ApoE were inversely and positively linked, respectively, to mortality rates.

Conclusion: In patients with ARIs, FBG level, rather than HbA1c level, is a risk factor for mortality. Moreover, low LDL/sdLDL levels and high ApoE levels are associated with increased mortality. The retrospective design and lack of long-term follow-up may limit the findings, highlighting the need for prospective validation.

Keywords: mortality, acute respiratory infection, blood glucose level, blood lipoproteins

Introduction

Every winter, as temperatures drop, the prevalence of acute respiratory diseases (ARIs) increases significantly, posing a great challenge to society and healthcare systems. The Global Burden of Disease study indicated that ARI-related deaths are second only to those caused by ischemic heart disease.[1] The World Health Organization estimates that, excluding global pandemics, 5–15% of the global population contracts seasonal influenza annually, leading to 3–5 million severe cases and 500,000 deaths.[2] Statistically, ARIs caused by the novel coronavirus have approached 772.39 million cases, with nearly 7 million deaths.[3] Consequently, there is an urgent need for early and reliable indicators to aid clinicians in risk stratification, prompt intervention, and the efficient allocation of medical resources.

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Studies have shown that the risk of mortality in patients with ARIs is significantly increased and is associated with diabetes mellitus (DM), especially poor glycemic control.[4] Additional studies have suggested that hyperglycemia is associated with mortality in patients with ARIs, regardless of whether they have DM.[5–8] The effects of acute dysglycemia, such as elevated fasting blood glucose (FBG), and chronic hyperglycemia, as indicated by glycated hemoglobin (HbA1c), on ARI-related mortality remain unclear, underscoring the need for multidimensional glycemic stratification in a particular study. Apart from blood glucose, little is known about the impact of blood lipids like ApoE and sdLDL on mortality in ARIs, and just a few studies have investigated the correlation between complete lipid profile and mortality in this context.[9–11] This study collected clinical data from 1675 patients and compared the clinical characteristics and laboratory indicators between recovered and deceased patients to explore the correlation between high FBG, HbA1c, blood lipids, and other indicators with mortality in patients with ARIs, providing important evidence for predicting the risk of death in these cases.

Methods

Study Design and Patients

This retrospective study involved 1786 patients with ARIs who were admitted to Shanghai Eighth People's Hospital between December 26, 2022, and January 31, 2023. The inclusion criteria were fever, cough, nasal congestion, rhinorrhea, sore throat, anosmia, ageusia, and fatigue, as well as CT findings indicative of pneumonia. A total of 1675 patients with ARIs were included and categorized into a recovery group (1425 patients) and a mortality group (250 patients) based on their clinical outcomes. The medical records of all patients during hospitalization, including demographic data, physical examinations, initial laboratory results, clinical diagnoses, and outcomes, were retrieved from the electronic health records. In clinical diagnostics, whole blood is utilized for measuring HbA1c and complete blood count. Plasma is the preferred sample type for assessing coagulation profiles. Serum is employed for a broad range of tests such as liver and renal function panels, cardiac enzymes, FBG, and blood lipoproteins. FBG is quantified using the hexokinase enzymatic assay, ensuring high specificity and accuracy. HbA1c analysis is performed via high-performance liquid chromatography with ion exchange. High-density lipoprotein (HDL) and low-density lipoprotein (LDL) levels are determined through homogeneous clearance assays, which selectively eliminate non-target lipoproteins prior to measurement. Triglycerides (TG), total cholesterol (TC), and small dense LDL (sdLDL) are analyzed using enzymatic colorimetric methods. Apolipoprotein E (ApoE) concentrations are measured via immunoturbidimetric assays. Liver function tests and renal function tests are primarily performed using enzymatic assays. Electrolytes are quantified via the ion-selective electrode method.

Statistical Analysis

Data processing was performed using SPSS 27.0 statistical software (IBM Corp., USA). Normally distributed measurement data are expressed as (x±s), and comparisons between groups were made using two-sample *t*-tests. Non-normally distributed measurement data were expressed as M(IQR), and comparisons between groups were performed using non-parametric tests. Counting data were expressed as [n(%)], and comparisons between groups were made using chi-square tests or Fisher's exact probability method. Propensity score matching was conducted using the Matchit package in R software, based on age and sex, with a 1:2 matching ratio between the two groups and a caliper width of 0.01. The clinical characteristics of recovered and deceased patients were compared. Variables with statistical differences ($p<0.05$) were introduced into a binary logistic regression equation to screen for risk factors for death due to ARIs. The association between each risk factor and the risk of death was quantified using adjusted odds ratios (OR) with 95% confidence intervals (CI). Furthermore, the identified risk factors for death were subgrouped and analyzed using binary logistic regression. The subgroup with the lowest mortality rate served as the reference group, and the association between each subgroup and death was quantified using OR with 95% CI. Statistical significance was set at $p<0.05$. Graphical representations were generated using Prism 9.0 (GraphPad Software, USA) and Origin 2021 software (OriginLab, USA).

Results

Comparison of Clinical Characteristics and Laboratory Findings Between Recovered and Deceased Patients in All Hospitalized Subjects

Among the 1675 patients, 1425 recovered and were discharged, with a median age of 72.0 years. Conversely, 250 patients died, with a median age of 86.0 years, which was significantly higher than that in the recovery group (p<0.001). The deceased group exhibited a notably higher proportion of males compared to the recovery group. Systolic blood pressure (SBP) in the deceased group was higher than that in the recovery group (p=0.008). The prevalence of chronic obstructive pulmonary disease (COPD), diabetes mellitus (DM), hypertension, coronary atherosclerotic heart disease, atrial fibrillation, acute kidney injury (AKI), chronic kidney disease (CKD), stroke, malignant tumors, and vascular dementia was significantly higher in the deceased group than in the recovery group (p<0.05) (Figure 1).

Upon admission, initial laboratory tests revealed significantly elevated levels of the following indicators in the deceased group compared with those in the recovered group: neutrophil percentage, C-reactive protein (CRP), creatine kinase (CK), red blood cell distribution width (RDW), blood urea nitrogen (BUN), lactate dehydrogenase (LDH), myoglobin (MYO), D-dimer, aspartate aminotransferase (AST), white blood cell count (WBC), serum amyloid A protein (SAA), neutrophil-to-lymphocyte ratio (NLR), creatine kinase isoenzyme, TG, ApoE, and FBG. In contrast, the following indicators were significantly lower in the deceased group: lymphocyte count (LYM), platelet count, mean hemoglobin concentration, albumin to globulin ratio (A/G), TC, sdLDL, apolipoprotein A1 (ApoA1), HDL, and LDL (p<0.05). There were no statistically significant differences in HbA1c, apolipoprotein B (ApoB), apolipoprotein A2 (ApoA2), or lipoprotein a (LPa) between the two groups (p>0.05) (Table 1).

Comparison of Clinical Characteristics and Laboratory Findings Between the Recovered and Deceased Patients in Age- and Sex-Matched Subjects

Significant differences in age and sex between the recovered and deceased groups could potentially bias the analysis of the risk factors for mortality. Therefore, 1:2 propensity score matching analysis was employed to balance these variables. Following propensity score matching, the median age in both groups was 86.0 years, with a male proportion of 64% (p>0.05). The comparison revealed that the deceased group had a lower BMI than the recovered group (p =0.041). Among the comorbidities, the prevalence of DM, AKI, and CKD was significantly higher in the deceased group than in the recovered group (p<0.05) (Figure 1). The laboratory test results of the two groups remained similar after propensity score matching.

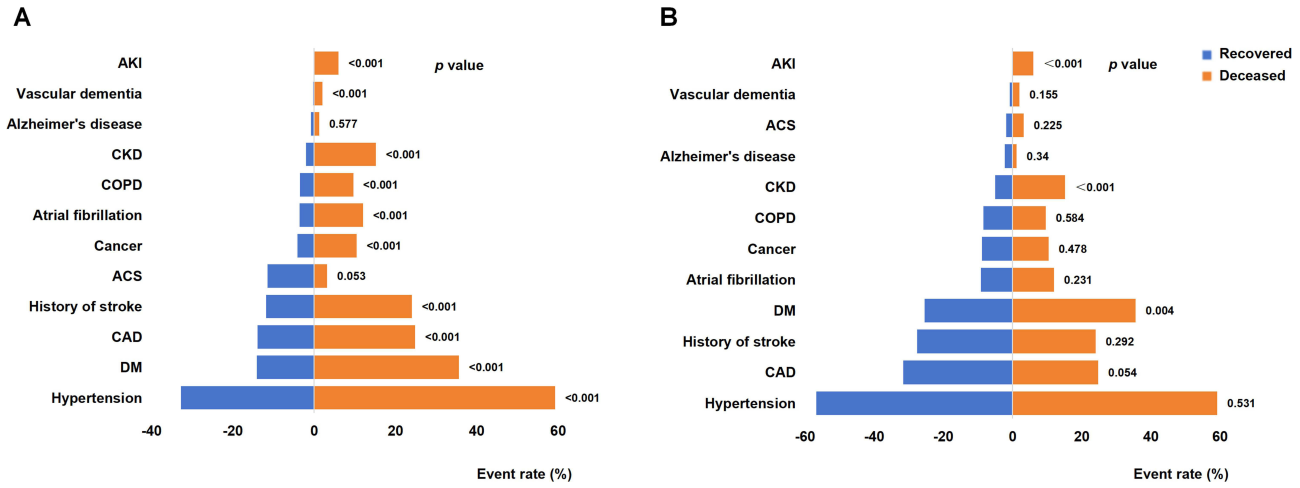

Figure 1 Comorbidities of patients. (**A**) Comorbidities of all patients. (**B**) Comorbidities of age- and sex-matched patients.

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Table 1 Clinical Features of Patients

	All Hospitalized Patients			Age- and Sex-Matched Patients		
Clinical Features	**Recovered (n=1425)**	**Deceased (n=250)**	***p* value**	**Recovered (n=500)**	**Deceased (n=250)**	***p* value**
Age (years)	72.0 (60.0–82.0)	86.0 (78.8–90.0)	<0.001	86.0 (79.0–89.0)	86.0 (78.8–90.0)	0.641
Sex, n (%)			0.001			1.000
Male	750 (52.6)	160 (64.0)		320 (64.0)	160 (64.0)	
Female	675 (47.4)	90 (36.0)		180 (36.0)	90 (36.0)	
BP (mmHg)						
SBP	130.0 (120.0–142.0)	135.0 (121.0–151.0)	0.008	137 (123–149)	135 (121–151)	0.537
DBP	78.0 (70.0–85.0)	76.5 (68.0–87.0)	0.343	77 (70–85)	77 (68–87)	0.706
BMI (kg/m^2)	23.4 (21.2–26.0)	22.1 (20.2–24.9)	0.240	23.3 (20.8–25.2)	21.9 (19.9–24.8)	0.041
Laboratory parameters						
Neutrophil percentage (%)	69.5 (60.3–78.1)	85.4 (78.7–90.8)	<0.001	73.7 (62.3–80.7)	85.4 (78.7–90.8)	<0.001
CRP (mg/L)	10.0 (0.8–40.6)	78.7 (35.7–132.5)	<0.001	22.1 (5.3–54.1)	79.9 (36.0–132.6)	<0.001
CK (u/L)	55.0 (34.0–106.0)	133.0 (63.3–453.5)	<0.001	60.0 (34.0–125.0)	137.5 (66.5, 473.0)	<0.001
RDW (fl)	41.3 (39.2–44.5)	44.7 (41.9–48.6)	<0.001	41.7 (39.8–45.0)	44.8 (41.5–48.5)	<0.001
BUN (mmol/L)	5.5 (4.2–7.2)	12.1 (7.9–18.7)	<0.001	6.5 (5.1–8.9)	12.1 (7.9–18.6)	<0.001
LDH (u/L)	210.5 (173.0–262.0)	342.0 (252.5–501.0)	<0.001	226.0 (188.0–286.0)	342.0 (252.5–501.0)	<0.001
MYO (ng/mL)	63.8 (38.5–121.9)	267.4 (128.0–567.5)	<0.001	90.4 (60.2–161.1)	273.0 (129.0–570.9)	<0.001
D-Dimer (mg/L)	1.3 (0.9–2.3)	3.5 (1.8–9.7)	<0.001	1.5 (1.0–2.7)	3.5 (1.8–9.7)	<0.001
LYM (10^9/L)	1.1 (0.8–1.6)	0.6 (0.4–1.0)	<0.001	1.0 (0.6–1.3)	0.6 (0.4–0.9)	<0.001
PLT (10^9/L)	214.0 (161.0–284.0)	163.0 (113.0–233.0)	<0.001	190.0 (139.8–250.0)	166.0 (114.0–236.0)	0.001
MCHC (g/L)	337.0 (330.0–344.0)	335.0 (325.5–341.5)	0.001	338.0 (330.0–346.0)	335.0 (325.0–342.0)	<0.001
AST (u/L)	31.0 (24.0–43.0)	44.0 (33.0–66.3)	<0.001	33.0 (24.0–44.0)	44.0 (33.0–67.8)	<0.001
WBC (10^9/L)	6.1 (4.6–8.0)	8.6 (6.1–12.1)	<0.001	5.9 (4.6–7.6)	8.6 (6.2–12.0)	<0.001
SAA (mg/L)	41.9 (8.0–179.2)	235.4 (122.4–316.6)	<0.001	85.0 (20.7–219.8)	235.5 (120.2–316.5)	<0.001
A/G	1.3 (1.1–1.4)	1.0 (0.9–1.1)	<0.001	1.1 (1.0–1.3)	1.0 (0.9–1.1)	<0.001
NLR	3.6 (2.2–6.1)	11.4 (6.2–19.2)	<0.001	4.6 (2.7–7.4)	11.6 (6.3–19.0)	<0.001
CKMB (u/L)	1.0 (0.6–2.1)	3.2 (1.4–6.1)	<0.001	1.3 (0.7–2.7)	3.2 (1.4–6.2)	<0.001
TG (mmol/L)	1.2 (0.9–1.6)	1.3 (1.0–1.6)	0.038	1.0 (0.8–1.4)	1.3 (1.0–1.6)	<0.001
TC (mmol/L)	4.15 (3.54–4.90)	3.74 (3.12–4.47)	<0.001	4.00 (3.34, 4.58)	3.75 (3.14–4.48)	0.145
sdLDL (mmol/L)	0.47 (0.35–0.63)	0.33 (0.23–0.42)	<0.001	0.41 (0.32, 0.55)	0.33 (0.24–0.42)	<0.001
ApoA1 (mmol/L)	1.1 (0.9–1.2)	0.9 (0.8–1.0)	<0.001	1.0 (0.9–1.2)	0.9 (0.8–1.0)	<0.001
HDL (mmol/L)	0.98 (0.81–1.18)	0.84 (0.68–1.03)	<0.001	0.96 (0.81–1.16)	0.85 (0.68–1.02)	0.002
LDL (mmol/L)	2.4 (1.9–2.9)	2.0 (1.5–2.4)	<0.001	2.2 (1.8–2.8)	2.0 (1.6–2.5)	0.011
ApoE (mmol/L)	45.5 (39.0–53.0)	54.0 (45.5–62.5)	<0.001	45.0 (39.0–52.0)	54.0 (45.8–62.3)	<0.001
ApoB (mmol/L)	0.82 (0.69–0.96)	0.80 (0.68–0.92)	0.180	0.80 (0.67–0.91)	0.81 (0.69–0.94)	0.688
LPa (mmol/L)	126.0 (73.0–234.3)	105.0 (68.0–217.0)	0.203	124.0 (69.5–224.0)	104.0 (71.8–217.3)	0.569
ApoA2 (mmol/L)	337.0 (288.0–416.0)	313.0 (275.0–375.0)	0.125	327.0 (274.0–383.5)	321.5 (275.8–376.3)	0.871
HbA1c (%)	6.3 (5.9–7.1)	6.5 (6.0–7.2)	0.160	6.4 (6.0–7.1)	6.5 (6.0–7.2)	0.580
FBG (mmol/L)	5.8 (5.0–7.0)	7.8 (6.3–10.5)	<0.001	5.8 (5.0–7.0)	7.8 (6.3–10.5)	<0.001

Note: All measurement data were expressed by median (IQR).

Abbreviations: BP, blood pressure; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; BMI, body mass index; ACS, acute coronary syndrome; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; CAD, coronary artery disease; AKI, acute kidney injury; CKD, chronic kidney disease; CRP, C-reactive protein; CK, creatine kinase; RDW, Red blood cell volume distribution width; BUN, blood urea nitrogen; LDH, lactate dehydrogenase; MYO, myoglobin; LYM, lymphocyte count; PLT, blood platelets; MCHC, mean corpuscular hemoglobin concentration; AST, aspartate aminotransferase; WBC, white blood cell count; SAA, serum amyloid A protein; A/G, albumin-to-globulin ratio; NLR, neutrophil-to-lymphocyte ratio; CKMB, creatine kinase-MB; TG, triglyceride; TC, total cholesterol; sdLDL, small dense low-density lipoprotein; ApoA1, apolipoprotein A1; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ApoE, apolipoprotein E; ApoB, apolipoprotein B; LPa, lipoprotein a; ApoA2, apolipoprotein A2; HbA1c, glycated hemoglobin; FBG, fasting blood glucose.

Binary Logistic Regression

Following propensity score matching, we categorized the statistically significant indicators into three distinct groups. Binary logistic regression analysis was conducted on all patients with ARIs. Our findings revealed that FBG, LDL, sdLDL, ApoE, D-dimer, LYM, BUN, and DM were risk factors associated with patient mortality in ARIs ($p<0.05$; Table 2).

Impact of FBG and HbA1c on Mortality

In the overall patient cohort, mortality rates exhibited a graded increase with higher FBG, rising from 4.0–4.9mmol/l in the lowest FBG group to above 7.8mmol/l in the highest. A similar trend was observed in the patients without DM (Figure 2A). Stratified analysis revealed that HbA1c levels between 5.7–6.4% and 6.5–8.4% were strongly associated with increased mortality ($p< 0.001$ for both). Mortality exhibited an ascending trend in correlation with elevated blood glucose levels in both groups. In contrast, the highest HbA1c category (≥8.5%) did not demonstrate a statistically significant mortality difference ($p=0.993$). It is also noteworthy that when FBG levels were ≥7.8 mmol/L, mortality displayed a parabolic relationship with increasing HbA1c levels ($p=0.020$; Figure 2B). A further key observation was that FBG demonstrated a "J"-shaped correlation with mortality in all patients (Table 3 and Figure 2C). Subgroup analysis of FBG revealed that the lowest mortality rate was observed when FBG levels were between 4.0–4.9 mmol/l, which served as the reference point. Mortality rates increased when FBG levels deviated from the reference range, either above or below. Specifically, when FBG levels were below 4 mmol/l, the mortality rate was 20.7%, representing a 7.16-fold increase in risk compared to the reference range (95% CI: 2.21–23.13, $p=0.001$). Conversely, when FBG levels were ≥ 11.1 mmol/l, mortality peaked at 39.3%, with a 17.78-fold increase in risk compared to the reference range (95% CI: 7.48–42.26, $p<0.001$). However, after adjusting for age and sex, no significant correlation between mortality and FBG levels was found when FBG levels were < 4 mmol/l.

In the patients without DM, FBG still presented a "J"-shaped correlation with mortality (Table 3 and Figure 2D). Among patients without DM, the lowest mortality rate of 3.0% was observed when FBG levels were within the range of 4.0–4.9 mmol/l, which was used as the reference point. When FBG levels were below 4 mmol/l, the mortality rate increased to 26.7%, with an 11.78-fold increased risk of death compared with the reference range ($p<0.001$). Furthermore, FBG exhibited a positive correlation with mortality when levels were ≥ 4.0 mmol/l. When FBG levels exceeded 7.8 mmol/l, mortality peaked at 29.3%, with a 13.46-fold increased risk of death compared with normoglycemic individuals ($p<0.001$). Even after adjusting for age and sex, this trend persisted, indicating an increase in mortality rates when FBG levels deviated from the reference range.

Table 2 Logistic Regression to Identify Independent Risk Factors of Mortality in All Patients

Group 1	*p* value	Group 2	*p* value	Group 3	*p* value
FBG	<0.001	ApoE	<0.001	LDH	0.062
D-Dimer	0.03	sdLDL	0.001	MYO	0.079
LDL	0.036	DM	0.006	CK	0.264
NEU	0.063	LYM	0.01	CKD	0.297
TG	0.067	Bun	0.027	BMI	0.301
Sex	0.339	A/G	0.094	WBC	0.401
MCHC	0.349	HDL	0.111	CKMB	0.421
NLR	0.375	PLT	0.727	SAA	0.441
AST	0.632	RDW	0.898	CRP	0.495
Age	0.999	Sex	0.981	ApoA1	0.754
AKI	0.999	Age	0.999	Sex	0.811

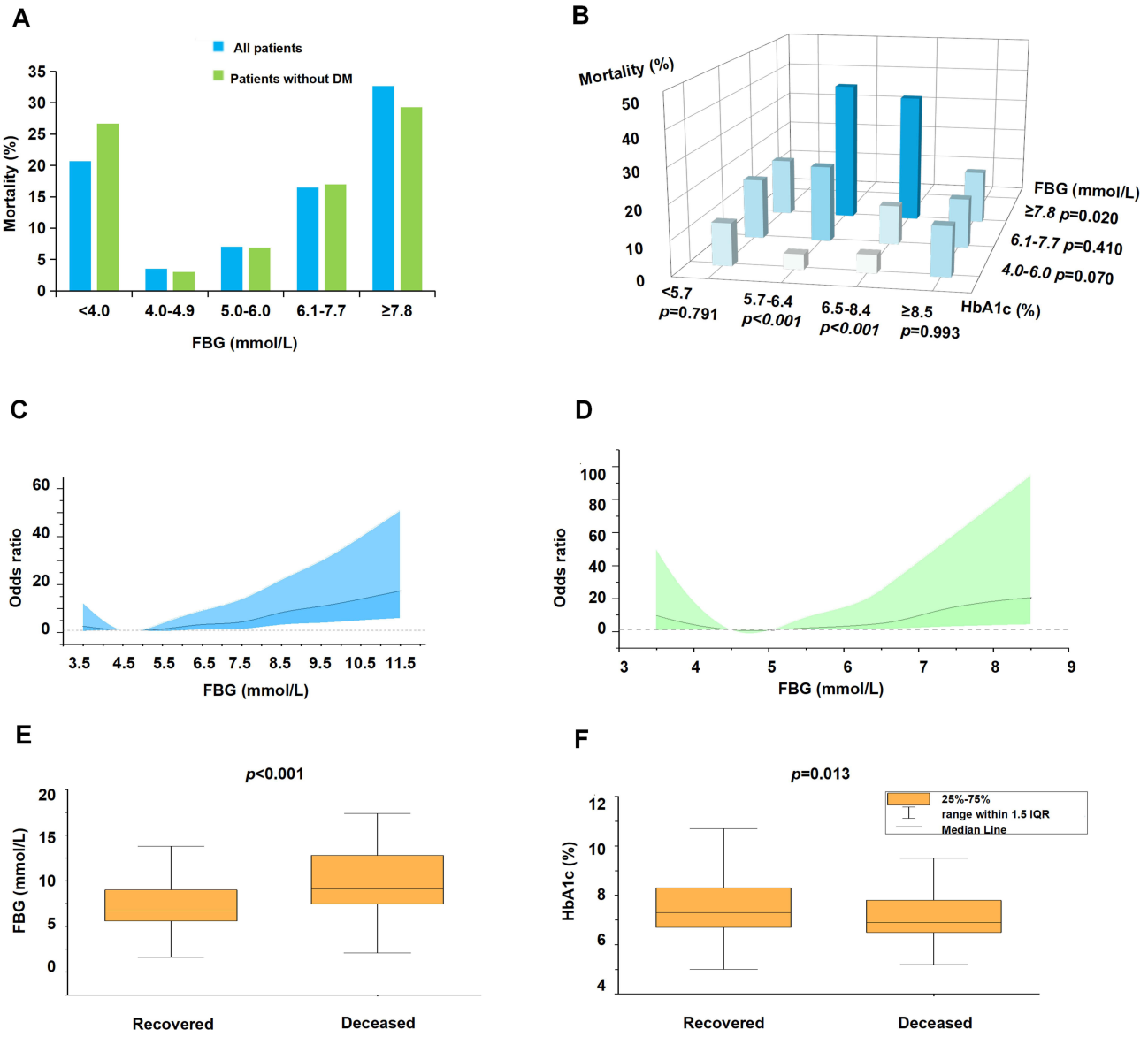

Figure 2 Mortality and partial effect plot of FBG and distribution of FBG and HbA1c of patients. (**A**) Shows mortality according to FBG among patients. (**B**) Shows the association between FBG and HbA1c of all patients. Partial effect plot of FBG-mortality of all patients (**C**) and FBG-mortality of patients without DM (**D**). Central lines represent the estimated adjusted odds ratios, with colored region denoting 95% CI. (**E** and **F**) Show the distribution of FBG and HbA1c of patients with DM.

Among patients with DM, the deceased group showed significantly higher FBG levels than the recovered group (p<0.001; Figure 2E). Additionally, HbA1c levels were notably lower in the deceased group than in the recovered group (p=0.013; Figure 2F).

Impact of Blood Lipoproteins and Other Biomarkers on Mortality

An inverse correlation between LDL and mortality was observed irrespective of age and sex adjustment (Figure 3A). The reference range for LDL, which is associated with the lowest mortality rate, was 2.6 to 3.3 mmol/l. Mortality increased as LDL levels decreased below 3.4 mmol/l, peaking at 32.8% when LDL levels were less than 1.4 mmol/l. Before and after adjustment for age and sex, the risk of death was 6.34-fold and 4.92-fold higher than that of the reference, respectively (Table 4). Among all patients, sdLDL exhibited an inverse correlation with mortality, with mortality significantly increasing when sdLDL was less than 0.30 mmol/l, peaking at 37.9% (shown in Figure 3B). This represented a 10.37-fold and 4.43-fold higher risk of death compared to the reference before and after adjustment, respectively (p<0.05).

Table 3 The Association of FBG with Mortality in Patients

	FBG (mmol/L)	Unadjusted Model OR (95% CI)	*p* value	Adjusted Model OR (95% CI)	*p* value
All patients	<4.0	7.16 (2.21–23.13)	0.001	2.66 (0.57–12.38)	0.214
	4.0–4.9	ref.		ref.	
	5.0–6.0	2.05 (0.87–4.81)	0.099	1.50 (0.56–4.02)	0.416
	6.1–6.9	4.92 (2.09–11.57)	<0.001	3.37 (1.23–9.28)	0.019
	7.0–7.7	6.48 (2.58–16.27)	<0.001	4.47 (1.42–14.07)	0.01
	7.8–11.0	11.45 (5.04–25.98)	<0.001	8.38 (3.17–22.16)	<0.001
	≥11.1	17.78 (7.48–42.26)	<0.001	17.43 (5.95–51.05)	<0.001
Patients without DM	<4.0	11.78 (2.77–50.21)	<0.001	9.70 (1.22–77.03)	0.032
	4.0–4.9	ref.		ref.	
	5.0–6.0	2.41 (0.89–6.52)	0.083	2.09 (0.63–6.94)	0.228
	6.1–7.7	6.62 (2.49–17.62)	<0.001	4.93 (1.47–16.55)	0.010
	≥7.8	13.46 (4.97–36.46)	<0.001	20.55 (4.19–100.89)	<0.001

Furthermore, ApoE levels were positively correlated with mortality (Figure 3C). Mortality peaked at 29.1% when ApoE levels were ≥60 mmol/l, with a 4.70-fold and 3.99-fold increased risk of death compared to the reference before and after adjustment, respectively ($p<0.001$).

After stratifying D-dimer, BUN, and LYM, D-dimer and BUN were positively correlated with mortality, and LYM was inversely correlated with mortality (Table 4).

Discussion

ARIs are classified into two main categories: upper respiratory tract infections (URI) and lower respiratory tract infections (LRI). The pathogenic microorganisms involved predominantly cause URI, with viruses accounting for 70–80% of cases, while viruses are implicated in approximately 60% of LRI.[12,13] This study, conducted during the winter season at Shanghai Eighth People's Hospital, aimed to predict mortality risk among patients admitted with ARIs.

Previous studies have indicated that DM and hyperglycemia are risk factors for mortality in patients with ARIs.[14–17] While our findings align with those reported in European/American/Australian cohorts, this consistency across diverse populations strengthens the robustness of the observed phenomenon.[18–20] The replication of results despite ethnic and environmental differences suggests that may be a universal mechanism. Notably, our study performed simultaneous stratified and grouped analyses of FBG and HbA1c levels and mortality. Our study found that among the entire hospitalized population, when FBG was ≥4.0 mmol/l, the higher the blood glucose level, the higher the mortality rate, which is similar to previous research results.[5,16,17] Some studies reported that there was no correlation between HbA1c and mortality from ARIs, whereas others found that low HbA1c was associated with low mortality.[21] This study is the first to show that when FBG is normal or mildly elevated (6.1–7.7 mmol/L), there is no correlation between HbA1c and mortality. However, when FBG level was ≥7.8 mmol/l, mortality exhibited a parabolic association with increasing

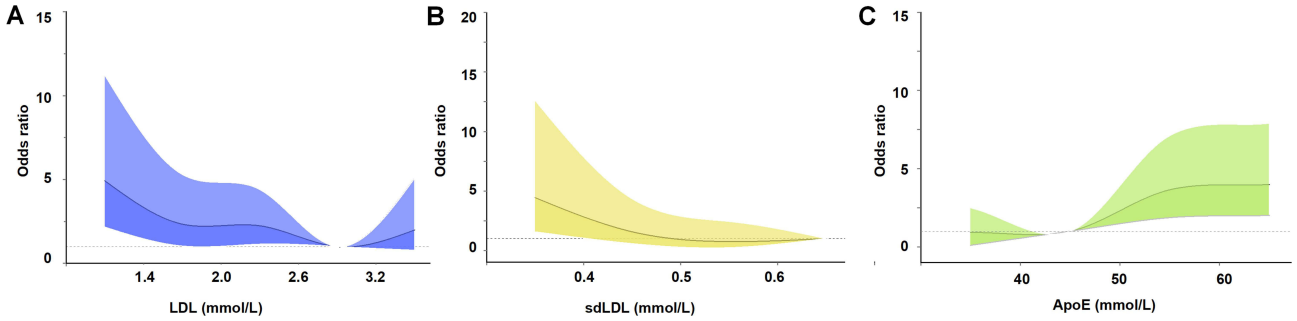

Figure 3 Partial effect plot of LDL, sdLDL and ApoE. Partial effect plot of LDL-mortality of all patients (**A**). Partial effect plot of sdLDL-mortality of all patients (**B**). Partial effect plot of ApoE-mortality of all patients (**C**).

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Table 4 Association of Laboratory Parameters with Mortality in All Patients

		Deaths/ Patients	Mortality (%)	Unadjusted Model OR (95% CI)	*p* value	Adjusted Model OR (95% CI)	*p* value
LDL (mmol/L)	<1.4	20/61	32.8	6.34 (2.92–13.80)	<0.001	4.92 (2.16–11.21)	<0.001
	1.4–1.7	15/91	16.5	2.57 (1.16–5.66)	0.019	2.34 (1.03–5.3)	0.043
	1.8–2.5	42/264	15.9	2.46 (1.28–4.73)	0.007	2.24 (1.14–4.40)	0.020
	2.6–3.3	13/182	7.1	Ref.		Ref.	
	≥3.4	9/83	10.8	1.58 (0.65–3.86)	0.315	1.99 (0.78–5.07)	0.151
sdLDL (mmol/L)	<0.30	36/95	37.9	10.37 (3.84–27.99)	<0.001	4.43 (1.56–12.60)	0.005
	0.30–0.49	36/238	15.1	3.03 (1.15–7.99)	0.025	1.57 (0.57–4.34)	0.383
	0.50–0.69	9/131	6.9	1.254 (0.41–3.87)	0.694	0.75 (0.23–2.44)	0.634
	≥0.70	5/90	5.6	Ref.		Ref.	
ApoE (mmol/L)	<40	13/147	8.8	1.11 (0.53–2.34)	0.783	0.92 (0.42–2.00)	0.827
	40–49	18/224	8.0	Ref.		Ref.	
	50–59	32/135	23.7	3.56 (1.91–6.64)	<0.001	3.65 (1.87–7.11)	<0.001
	≥60	30/103	29.1	4.70 (2.47–8.94)	<0.001	3.99 (2.01–7.91)	<0.001
D-Dimer (mg/L)	<0.81	3/239	1.3	Ref.		Ref.	
	0.81–1.19	11/283	3.9	3.18 (0.88–11.54)	0.078	0.59 (0.09–3.67)	0.568
	1.20–1.89	45/305	14.8	13.62 (4.18–44.39)	<0.001	2.63 (0.57–12.01)	0.213
	1.90–3.99	66/275	24.0	24.84 (7.70–80.19)	<0.001	6.83 (1.53–30.45)	0.012
BUN (mmol/L)	≥4.00	106/247	42.9	59.14 (18.42–189.84)	<0.001	15.00 (3.38–66.57)	<0.001
	<4.00	6/278	2.2	Ref.		Ref.	
	4.00–5.24	15/307	4.9	2.33 (0.89–6.09)	0.085	5.51 (0.66–46.17)	0.116
	5.25–6.89	26/376	6.9	3.37 (1.37–8.30)	0.008	6.96 (0.89–54.53)	0.065
	6.90–11.09	62/299	20.7	11.86 (5.04–27.91)	<0.001	10.14 (1.32–78.08)	0.026
	≥11.10	136/266	51.1	47.43 (20.40–110.28)	<0.001	50.26 (6.69–377.65)	<0.001
LYM (10^9/L)	<0.5	64/103	62.1	16.96 (4.86–59.20)	<0.001	19.04 (2.24–161.80)	0.007
	0.5–0.7	75/169	44.4	8.25 (2.43–28.02)	<0.001	7.67 (0.95–61.89)	0.056
	0.8–1.2	67/228	29.4	4.30 (1.27–14.55)	0.019	4.67 (0.58–37.26)	0.146
	1.3–1.8	18/103	17.5	2.19 (0.60–7.95)	0.234	2.39 (0.27–21.51)	0.437
	≥1.9	3/34	8.8	Ref.		Ref.	

HbA1c level (p=0.020). This correlation may be attributed to the fact that HbA1c levels exceeding 8.5% suggest sustained hyperglycemia for at least three months, allowing the body to adapt. Acute hyperglycemia following ARIs does not exacerbate its impact on the body. In contrast, when HbA1c levels are normal or mildly elevated, mortality increases with increasing FBG levels. This implies that in patients with good glycemic control, a sudden surge in FBG levels may signify severe stress and indicates that glucose toxicity from acute hyperglycemia contributes significantly to mortality from ARIs.[5] However, the specific mechanisms require further investigation.

Some studies have demonstrated that patients with ARIs exhibit decreased LDL-C levels.[22] Our study found that in patients with LDL levels below 3.4 mmol/L, a lower LDL level was associated with a higher mortality rate among those with ARIs, consistent with previous research.[22] However, no significant correlation was observed between LDL levels and mortality when the LDL levels were ≥3.4 mmol/L. The precise pathophysiological role of lipoproteins in ARIs remains unclear.[23,24] Previous research suggests that lipoproteins play a pivotal role in clearing pathogen-related lipids and toxins during severe infections such as sepsis.[25] Consequently, the lower lipid levels observed in individuals with fatal ARIs may indicate an impaired antiviral capacity. Alternatively, elevated lipid levels may indicate a generally healthier state, as low plasma lipid levels are often associated with hypermetabolism and malnutrition in infected patients.[25]

Currently, there is limited information regarding the relationship between sdLDL levels and mortality in patients with ARIs. A previous study proposed that an increase in sdLDL levels may be associated with disease severity.[18] However, a conflicting report has suggested that sdLDL levels were lower in deceased individuals than in those who recovered.[26] sdLDL refers to particles with a peak diameter of less than 25.8 nm and increased density.[27] Normally considered a risk factor for atherosclerosis, elevated sdLDL levels are closely associated with the development and progression of cardiovascular and cerebrovascular diseases. However, our study found that lower sdLDL levels were associated with higher mortality rates. Although oxidized sdLDL (ox-LDL) is pro-inflammatory, its reduction might attenuate the activation of antioxidant defense systems, resulting in inadequate immune responses to infections.[28] Besides, cellular membrane lipid rafts rely on cholesterol for structural integrity.[29] A decline in sdLDL could impair signaling in immune cells (eg, T cells, B cells), reducing antiviral or antibacterial efficacy. Reduced sdLDL often accompanies hypocholesterolemia, seen in malnutrition or chronic inflammatory states (eg, cancer, liver disease). Low cholesterol may destabilize cell membranes and impair hormone synthesis, leading to immunosuppression. Researchers underscores the need for further investigation of the mechanisms by which sdLDL influences immune regulation, antiviral effects, and other related aspects.

This study revealed a significant correlation between increased ApoE levels and mortality rates associated with ARIs. In a previous study, patients with severe pneumonia had lower plasma APOE levels than non-severe patients,[30] but no comparison was made between patients who died from ARIs and those who recovered. ApoE is involved in lipid metabolism and has important immune regulatory functions, including the inhibition of T cell activation and proliferation, regulation of macrophage function, and promotion of CD1-mediated lipid antigen presentation. Its abnormal elevation may disrupt lipid balance in macrophages, leading to intracellular lipid accumulation (eg, foam cell formation) and impairing their ability to phagocytose pathogens. Furthermore, ApoE may modulate cytokine release (eg, Interleukin-6, Tumor Necrosis Factor-alpha), exacerbating inflammation. Excessive inflammation could trigger a "cytokine storm", worsening lung tissue damage, while suppressed inflammation might hinder pathogen clearance. Moreover, elevated ApoE may reflect impaired clearance of Very Low-Density Lipoprotein remnants, increasing circulating free fatty acids and inducing lipotoxicity.[31] Lipotoxicity can damage alveolar epithelial cells, worsening pulmonary edema and oxygenation. Human ApoE protein has three subtypes, ApoE2, ApoE3, and ApoE4, which exhibit functional polymorphisms. ApoE4 is associated with increased susceptibility to herpes simplex virus type 1 and HIV infections, and affects the incidence and progression of ARIs.[32] Furthermore, studies have shown that the C-terminal region of serum ApoE interacts with the receptor-binding domain of the SARS-CoV-2 spike protein, resulting in significant structural alterations in ApoE, which activates its metabolic pathway and facilitates viral infection.[33] ApoE4 is also associated with microglial dysfunction in Alzheimer's disease, suggesting a broader impact on immune cell clearance functions. The specific role of ApoE in the pathophysiology of ARIs merits further investigation.

Given the potential role of metabolic dysregulation in ARI progression, clinicians should prioritize monitoring lipid profiles and glucose levels as prognostic markers. Additionally, future research should investigate targeted interventions for high-risk ARI patients to mitigate adverse outcomes.

This study has several limitations. As all data were collected over a single winter season, the generalizability of the findings to other seasons remains uncertain. As the study focused on hospitalized patients and compared deceased and recovered patients only, additional research is required to elucidate the roles of FBG, LDL, sdLDL, and ApoE in the progression and prognosis of ARIs. Moreover, its single-center design risks selection bias, necessitating multi-center validation. Furthermore, the absence of long-term follow-up obscures the trajectory of post-ARI metabolic dysfunction, warranting extended monitoring in future work. Future prospective studies incorporating standardized microbiological testing protocols would be valuable to investigate potential pathogen-specific metabolic effects and validate our findings across different infectious etiologies.

Conclusions

This study found that FBG, LDL, sdLDL, and ApoE were risk factors for death from ARIs. FBG and ApoE were positively correlated with mortality from ARIs, while LDL and sdLDL were inversely correlated with mortality. This finding suggests important evidence for predicting the risk of death from ARIs.

Data Sharing Statement

The data supporting the findings of this study are accessible from the corresponding author (Jun Yin) upon request.

Ethics Approval and Informed Consent

The study was reviewed and approved by the Ethics Review Committee of Shanghai Eighth People's Hospital (approval number: 2024-081-13). As this was a retrospective study involving only anonymized medical record review without any patient intervention or additional risk, the Ethics Committee waived the requirement for individual patient consent. All data were de-identified and analyzed in strict compliance with the Declaration of Helsinki. Patient confidentiality was protected through secure data management protocols, with access restricted to authorized researchers only.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no conflicts of interest to declare in this work.

References

1. GBD 2021 Causes of Death Collaborators. Global burden of 288 causes of death and life expectancy decomposition in 204 countries and territories and 811 subnational locations, 1990–2021: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet*. 2024;403 (10440):2100–2132. doi:10.1016/S0140-6736(24)00367-2
2. Liu C, Hu L, Dong G, et al. Emerging drug design strategies in anti-influenza drug discovery. *Acta Pharm Sin B*. 2023;13(12):4715–4732. doi:10.1016/j.apsb.2023.08.010
3. World Health Organization. Coronavirus disease (COVID-19) pandemic [EB/OL]. 2023. Available from: https://covid19.who.int/. Accessed June 23, 2025.
4. Singh A, Khunti K. Assessment of risk, severity, mortality, glycemic control and antidiabetic agents in patients with diabetes and COVID-19: a narrative review. *Diabetes Res Clin Pract*. 2020;165:108266. doi:10.1016/j.diabres.2020.108266
5. van Herpt T, van Rosmalen F, Hulsewé H, et al. Hyperglycemia and glucose variability are associated with worse survival in mechanically ventilated COVID-19 patients: the prospective Maastricht Intensive Care Covid Cohort. *Diabetol Metab Syndr*. 2023;15(1):253. doi:10.1186/s13098-023-01228-1
6. Barbosa M, Marques-Sá J, Carvalho C, et al. Is elevated blood glucose at admission associated with poor outcomes in hospitalized COVID-19 patients? *Arch Endocrinol Metab*. 2023;67(6):e000649. doi:10.1016/j.diabet.2020.08.004
7. Yang P, Wang N, Wang J, et al. Admission fasting plasma glucose is an independent risk factor for 28-day mortality in patients with COVID-19. *J Med Virol*. 2021;93(4):2168–2176. doi:10.1002/jmv.26608
8. Xie W, Wu N, Wang B, et al. Fasting plasma glucose and glucose fluctuation are associated with COVID-19 prognosis regardless of pre-existing diabetes. *Diabetes Res Clin Pract*. 2021;180:109041. doi:10.1016/j.diabres.2021.109041
9. Veronica G, Walter V, Tommaso C, et al. COVID-19: a complex disease with a unique metabolic signature. *PLoS Pathog*. 2023;19(11). doi:10.1371/journal.ppat.1011787
10. Samantha L, Nathan GL, Nicola G, et al. Integrative plasma metabolic and lipidomic modelling of SARS-CoV-2 infection in relation to clinical severity and early mortality prediction. *Int J Mol Sci*. 2023;24(14). doi:10.3390/ijms241411614
11. Veronica G, Valentina P, Tommaso C, et al. Metabolomic and lipoproteomic differences and similarities between COVID-19 and other types of pneumonia. *Sci Rep*. 2025;15(1). doi:10.1038/s41598-025-91965-2
12. Woodhead M, Blasi F, Ewig S, et al. Guidelines for the management of adult lower respiratory tract infections--full version. *Clin Microbiol Infect*. 2011;17 Suppl 6(Suppl 6):E1–59. doi:10.1111/j.1469-0691.2011.03672.x

13. Charlton C, Babady E, Ginocchio C, et al. Practical guidance for clinical microbiology laboratories: viruses causing acute respiratory tract infections. *Clin Microbiol Rev*. 2019;32(1). doi:10.1128/CMR.00042-18
14. Jordan R, Adab P, Cheng K. Covid-19: risk factors for severe disease and death. *BMJ*. 2020;368:m1198. doi:10.1136/bmj.m1198
15. Zhang Y, Li H, Zhang J, et al. The clinical characteristics and outcomes of patients with diabetes and secondary hyperglycaemia with coronavirus disease 2019: a single-centre, retrospective, observational study in Wuhan. *Diabetes Obes Metab*. 2020;22(8):1443–1454. doi:10.1111/dom.14086
16. Zhu L, She Z, Cheng X, et al. Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type 2 diabetes. *Cell Metab*. 2020;31(6):1068–77.e3. doi:10.1016/j.cmet.2020.04.021
17. Zhao Y, Xing H. Influence of fasting plasma glucose level on admission of COVID-19 patients: a retrospective study. *J Diabetes Res*. 2022;2022:7424748. doi:10.1155/2022/7424748
18. Unjali G, Lauren TV, Abhinav G, et al. Association among diabetes, cardiovascular disease and mortality in patients hospitalised for COVID-19: an analysis of the American Heart Association COVID-19 CVD Registry. *BMJ Open*. 2024;14(12). doi:10.1136/bmjopen-2024-084087
19. Khunti K, Aroda V, Aschner P, et al. The impact of the COVID-19 pandemic on diabetes services: planning for a global recovery. *Lancet Diabetes Endocrinol*. 2022;10(12):890–900. doi:10.1016/S2213-8587(22)00278-9
20. Plummer M, Rait L, Finnis M, et al. Diabetes mellitus, glycaemic control, and severe COVID-19 in the Australian critical care setting: a nested cohort study. *Aust Crit Care*. 2023;36(4):579–585. doi:10.1016/j.aucc.2022.05.002
21. Tsikala Vafea M, Traboulsi C, Stefanovic-Racic M. Lower glycosylated hemoglobin is associated with lower in-hospital mortality in patients with COVID-19: a systematic review of the literature and meta-analysis. *Endocr Pract*. 2024;30(1):70–77. doi:10.1016/j.eprac.2023.09.009
22. Wang G, Zhang Q, Zhao X, et al. Low high-density lipoprotein level is correlated with the severity of COVID-19 patients: an observational study. *Lipids Health Dis*. 2020;19(1):204. doi:10.1186/s12944-020-01382-9
23. Mink S, Saely C, Frick M, et al. Association between lipid levels, Anti-SARS-CoV-2 spike antibodies and COVID-19 mortality: a prospective cohort study. *J Clin Med*. 2023;12(15):5068. doi:10.3390/jcm12155068
24. Abu-Farha M, Thanaraj T, Qaddoumi M, et al. The role of lipid metabolism in COVID-19 virus infection and as a drug target. *Int J Mol Sci*. 2020;21(10):3544. doi:10.3390/ijms21103544
25. Trinder M, Boyd J, Brunham L. Molecular regulation of plasma lipid levels during systemic inflammation and sepsis. *Curr Opin Lipidol*. 2019;30(2):108–116. doi:10.1097/MOL.0000000000000577
26. Ouyang S, Zhu H, Xie Y, et al. Temporal changes in laboratory markers of survivors and non-survivors of adult inpatients with COVID-19. *Bmc Infect Dis*. 2020;20(1):952. doi:10.1186/s12879-020-05678-0
27. El-Khoury J, Remaley A, Nordestgaard B, et al. Perspectives on the changing landscape of measuring cardiovascular risk related to LDL. *Clin Chem*. 2019;65(12):1487–1492. doi:10.1373/clinchem.2019.307306
28. Yunxiong W, Yuan J, Jingjing Z, et al. CD36-mediated uptake of oxidized LDL induces double-negative regulatory T cell ferroptosis in metabolic dysfunction-associated steatotic liver disease. *Metabolism*. 2025;164. doi:10.1016/j.metabol.2024.156127
29. Sin Man L, Chao Z, Zehua W, et al. A multi-omics investigation of the composition and function of extracellular vesicles along the temporal trajectory of COVID-19. *Nat Metab*. 2021;3(7). doi:10.1038/s42255-021-00425-4
30. Nguyen M, Bourredjem A, Piroth L, et al. High plasma concentration of non-esterified polyunsaturated fatty acids is a specific feature of severe COVID-19 pneumonia. *Sci Rep*. 2021;11(1):10824. doi:10.1038/s41598-021-90362-9
31. Meenakshi S, Zemin Y. Intrahepatic role of exchangeable apolipoproteins in lipoprotein assembly and secretion. *Arterioscler Thromb Vasc Biol*. 2012;32(5). doi:10.1161/ATVBAHA.111.241455
32. Chen F, Ke Q, Wei W, et al. Apolipoprotein E and viral infection: risks and mechanisms. *Mol Ther Nucl Acids*. 2023;33:529–542. doi:10.1016/j.omtn.2023.07.031
33. Yin Y, Sheng Y, Wang M, et al. Interaction of serum proteins with SARS-CoV-2 RBD. *Nanoscale*. 2021;13(30):12865–12873. doi:10.1039/d1nr02687a