Atherogenic Dyslipidemia on Admission Is Associated With Poorer Outcome in People With and Without Diabetes Hospitalized for COVID-19

Alfonso Bellia,[1,2] Aikaterini Andreadi,[1,2] Luca Giudice,[1,2] Sofia De Taddeo,[1,2] Alessio Maiorino,[1,2] Ilenia D'Ippolito,[1,2] Federica Maria Giorgino,[3] Valeria Ruotolo,[2] Maria Romano,[2] Andrea Magrini,[4] Nicola Di Daniele,[1] Paola Rogliani,[2,5] and Davide Lauro[1,2]

Diabetes Care 2021;44:1–9 | https://doi.org/10.2337/dc20-2838

OBJECTIVE

Identifying metabolic factors associated with critical disease can help to improve management of patients hospitalized for coronavirus disease 2019 (COVID-19). High triglycerides and low HDL levels characterize the atherogenic dyslipidemia closely related to insulin resistance and diabetes. We examined associations of atherogenic dyslipidemia detected on admission with outcome of COVID-19 during hospitalization.

RESEARCH DESIGN AND METHODS

We retrospectively analyzed clinical reports of 118 consecutive patients hospitalized for COVID-19 in Rome, Italy, between March and May 2020. Clinical characteristics, inflammation markers, and glucose and lipid metabolism parameters at admission were collected. Critical disease was defined as in-hospital death or need for endotracheal intubation. Associations were tested using logistic regression analysis.

RESULTS

Patients with critical COVID-19 ($n = 43$) were significantly older than those with noncritical disease ($n = 75$) and presented higher levels of fasting glucose, triglycerides, C-reactive protein, interleukin-6, procalcitonin, and D-dimer ($P < 0.01$ for all), whereas HDL levels were lower ($P = 0.003$). Atherogenic dyslipidemia was more frequent in patients with critical COVID-19 (46 vs. 24%, $P = 0.011$), as well as diabetes (37 vs. 19%, $P = 0.026$), and significantly associated with death or intubation (odds ratio 2.53 [95% CI 1.16–6.32], $P = 0.018$). Triglycerides were significantly associated with selected inflammatory biomarkers ($P < 0.05$ for all) and poorer outcome of COVID-19 during hospitalization in both the overall population and the subgroup with atherogenic dyslipidemia.

CONCLUSIONS

Atherogenic dyslipidemia detected on admission can be associated with critical in-hospital course of COVID-19. Further investigations are needed to elucidate the hypothetical role of insulin resistance and related lipid abnormalities in severe acute respiratory syndrome coronavirus 2 pathogenesis. Assessment of lipid profile should be encouraged in patients hospitalized for COVID-19.

The coronavirus disease 2019 (COVID-19) pandemic represents one of the greatest public health challenges in recent years. Identification of risk factors for poor prognosis

[1]Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy
[2]Division of Endocrinology and Diabetes, Fondazione Policlinico Tor Vergata, Rome, Italy
[3]Division of Respiratory Medicine, Fondazione Policlinico Tor Vergata, Rome, Italy
[4]Department of Biomedicine and Prevention, University of Rome Tor Vergata, Rome, Italy
[5]Department of Experimental Medicine, University of Rome Tor Vergata, Rome, Italy

Corresponding author: Davide Lauro, d.lauro@med.uniroma2.it

Received 20 November 2020 and accepted 27 May 2021

Diabetes Care Publish Ahead of Print, published online July 12, 2021

of COVID-19 is a key task in order to minimize morbidity and mortality attributable to the disease (1,2). Several metabolic abnormalities have been reported in patients with confirmed COVID-19, often related to the severity of disease, generating the hypothesis of a putative role in the pathogenesis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Accordingly, it is largely reported that patients with diabetes with COVID-19, especially when obesity is associated, are at increased risk of dying or requiring intensive care (3–5). In general, chronic hyperglycemia is an independent predictor for poor prognosis in lower respiratory tract infections (6), especially when established micro- and macrovascular complications have already occurred (7). Available evidence demonstrates that diabetes is a key risk factor for infectious disease and that individuals with diabetes have increased risk of infection-related mortality (8). Apart from lack of glucose control and coexisting complications of diabetes, which necessarily contribute to the inherent predisposition to illness of patients with diabetes, concomitant insulin resistance may accompany the severe forms of COVID-19 because insulin resistance is closely linked to systemic inflammation, prothrombotic state, vascular dysfunction, and impaired immune response (9–11). Altogether, these pathophysiological abnormalities potentially contribute to the metabolic overinflammation state (12) reported in patients with a more severe course of COVID-19 (13–15). Although knowledge about insulin resistance could be useful to improve risk assessment of a complicated course of disease in patients with severe COVID-19, its direct measurement is not easy to perform in clinical practice or, especially, in the hospital setting. In addition to overweight, a common feature strongly related to insulin resistance is the so-called atherogenic dyslipidemia, namely, the co-occurrence of hypertriglyceridemia, low HDL, and small-dense LDL particles (16). Indeed, it is the effect of insulin resistance on the assembly and secretion of VLDL, apolipoprotein B, and triglycerides that plays a pivotal role in the development of atherogenic dyslipidemia. Assessment of triglycerides and HDL is common in routine practice and may help easily identify lipidic derangements attributable to insulin resistance. To what extent presence of hypertriglyceridemia or low HDL can be associated with poorer outcome of COVID-19 during hospitalization, independently of BMI and preexisting diabetes, has not been determined yet. According to this background, we reviewed clinical records of patients admitted to our university hospital with confirmed diagnosis of COVID-19, aiming to explore potential association between atherogenic dyslipidemia detected on admission and course of the disease during hospitalization.

RESEARCH DESIGN AND METHODS

Study Design and Participants

We performed an observational retrospective analysis of data collected during the COVID-19 emergency in Italy between March and May 2020. We included 118 consecutive adult patients, who had presented to the emergency room (ER) of Policlinico Tor Vergata university hospital with symptoms suggestive of SARS-CoV-2 infection and subsequently referred to the Pulmonary and Endocrinology Unit with laboratory-confirmed diagnosis (by SARS-CoV-2 real-time PCR test in respiratory specimens) and clinical/radiological manifestations of disease (namely, ground-glass opacity and/or crazy paving on chest computed tomography). Policlinico Tor Vergata was one of the mandatorily designed COVID-19 hospitals in the urban area of Rome for care and treatment of patients with confirmed diagnosis of SARS-CoV-2 infection who required hospitalization. All patients received standard treatment according to local practice, including respiratory support (nasal cannulation, mask oxygenation, high-flow nasal cannula oxygen therapy, noninvasive positive pressure ventilation, or invasive mechanical ventilation), antimicrobial therapy to prevent or treat secondary infections, and nutritional and other supportive treatments as needed. Specific therapies for SARS-CoV-2 included empirical off-label administration of hydroxychloroquine, low-molecular-weight heparin, and antivirals (lopinavir/ritonavir or darunavir/ritonavir) and tocilizumab, when tolerated and not contraindicated. Authors of this article had been directly involved in the in-hospital care of patients eventually included in the analysis. Given the retrospective design, the present analysis did not interfere with course of medical management. The protocol was designed in accordance with the principles of Declaration of Helsinki for studies in humans. All patients gave informed consent to participate. The institutional ethics committee of Policlinico Tor Vergata university hospital reviewed and approved this study protocol.

Data Collection and Outcomes

Data were extracted by researchers themselves from electronic clinical records of the hospital. Clinical data for the following were analyzed: age; sex; ethnicity; weight; height; BMI; time (days) between onset of symptoms and presentation to the ER; ongoing medications prior to admission; presence of diabetes, hypertension, cardiovascular diseases, chronic obstructive pulmonary disease (COPD), and atherogenic dyslipidemia; and off-label administration of hydroxychloroquine, antivirals (lopinavir/ritonavir or darunavir/ritonavir), and tocilizumab during hospital stay. Biochemical data at the time of admission included total blood count, C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), procalcitonin, D-dimer, creatinine, estimated glomerular filtration rate (eGFR) according to Chronic Kidney Disease Epidemiology Collaboration equation (17), 25-hydroxyvitamin D (25-OH-vitamin D), total cholesterol, HDL, LDL, triglycerides, fasting glucose, and glycated hemoglobin (HbA_{1c}). The date of disease onset was defined as the day when symptoms suggestive of COVID-19 were first noticed. Time (days) between onset of symptoms and presentation to the ER was calculated for each individual. Presence of cardiovascular diseases was defined as patients having coronary heart disease, arrhythmias, or heart failure, according to reported medical history or ongoing medications. Presence of diabetes was assessed if patients were taking glucose-lowering medications (both insulin and noninsulin agents) or had HbA_{1c} levels $\geq$48 mmol/mol (18). In addition, presence of hypertension and COPD was defined by patients taking antihypertensives or bronchodilators, respectively. Finally, atherogenic dyslipidemia was defined as a combination of triglycerides $\geq$1.7 mmol/L (or on drug treatment for elevated triglycerides) and HDL $\leq$1.03 mmol/L in men and $\leq$1.3 mmol/L in women (19).

In accordance with previous studies (20,21), the composite of in-hospital death or admission to intensive care unit (ICU) with need for endotracheal

intubation was considered as the primary outcome measure to define critical COVID-19. The need for intubation was determined on the basis of clinical presentation in patients receiving full care throughout their hospitalization. As opposite, patients discharged without need for ICU admission were classified as having noncritical COVID-19. According to these criteria, all consecutive individuals included in this analysis had a definitive outcome (died, admitted to ICU, or discharged).

Statistical Analysis

Statistical analysis was performed with the SPSS version 25.0 software (IBM Corporation, Chicago, IL). Mean ± SD or median (interquartile range) were used as descriptive statistics for normally distributed or skewed continuous variables, respectively. Categorical variables were expressed as absolute and percent values. All quantitative variables were tested for normality distribution using the Kolmogorov-Smirnov test, and continuous parameters with a nonnormal distribution were logarithmically transformed before being used in the subsequent parametric procedures. Differences in continuous variables between critical and noncritical COVID-19 groups were assessed using *t* test for unpaired data. Differences in proportions of discrete traits were assessed using χ^2 and Fisher exact test. Potential associations of quantitative and qualitative parameters with the selected composite outcome (death or ICU admission) were first analyzed using univariate logistic regression analysis, and odds ratios (ORs) with 95% CIs were given to measure strength of the relationships. The following variables were initially assessed: age, sex, days to ER admission, BMI, serum CRP, IL-6, TNF-α, procalcitonin, D-dimer, eGFR, 25-OH-vitamin D, total and HDL and LDL cholesterol, triglycerides, fasting glucose, and presence of diabetes, atherogenic dyslipidemia, hypertension, cardiovascular disease, and COPD. Variables with $P < 0.05$ were regarded as potential predictors and included in the multivariate regression analysis using the stepwise bidirectional selection model (significance level to entry = 0.05; significance level to stay = 0.1). Age and sex were also included in the multivariate analysis. HDL cholesterol was not entered in the model to avoid the collinear effect with triglycerides. Regression analysis of parameters associated with the composite outcome was repeated in a subgroup with atherogenic dyslipidemia ($n = 38$). Additional sensitivity analysis was performed for mortality or need for intubation, considered separately, in both the overall population and the subgroup with atherogenic dyslipidemia. Finally, we tested the relationship between serum triglycerides and selected inflammation markers (CRP, D-dimer, procalcitonin) at hospital admission, using linear regression analysis, and resulting Spearman coefficients (ρ) were provided to evaluate strength of the associations. For all of these analyses, $P < 0.05$ based on the two-sided test was considered statistically significant.

RESULTS

Characteristics of Study Population

Baseline clinical characteristics of the study population, stratified according to outcome of disease during hospitalization (critical or noncritical), are shown in Table 1. All individuals were White Europeans, mean ± SD age 68.1 ± 15.5 years, and 38% were women. Most patients were overweight, with BMI 27.5 ± 3.8, but <8% of them were classifiable as obese (BMI >30 kg/m^2). The most common comorbidity was hypertension (45%).

Of 118 patients, 35 died (29.6%) and 43 (36.4%) met the composite outcome of in-hospital death or admission to ICU. The other 75 patients had better outcomes of disease and were discharged without need of intensive care during hospitalization. Patients with critical COVID-19 were substantially older (mean ± SD age 74.9 ± 11.1 vs. 64.2 ± 16.3 years, $P < 0.001$) and reported a shorter median time from onset of symptoms to ER admission (2.5 vs. 6 days, $P = 0.013$). No significant differences were observed in sex and mean BMI. As expected, plasma levels of CRP, IL-6, procalcitonin, and D-dimer, reflecting the severity of the disease, were significantly higher in patients with critical COVID-19 ($P < 0.01$ for all). In addition (22), baseline median levels of 25-OH-vitamin D were significantly lower in patients with subsequent worse prognosis ($P = 0.001$). Diabetes was also more frequent in the group with critical COVID-19 (37 vs. 19%, $P = 0.026$), while HbA_{1c} levels were not dissimilar between the two groups (6.3 ± 1.7 vs. 6.5 ± 1.8% [44 ± 12 vs. 48 ± 13 mmol/mol], $P = 0.53$). New cases of diabetes were not detected. Previous insulin therapy was also not dissimilar between COVID-19 patients with diabetes with poorer and better in-hospital outcomes (12 vs. 14%, respectively), with most patients in both groups being on one or two oral hypoglycemic agents prior the admission. In contrast with previous reports (2,5), no significant differences according to the outcome of disease were observed in prevalence of hypertension, COPD, or cardiovascular diseases. Noteworthy, admission levels of triglycerides, LDL, and HDL, were significantly impaired ($P < 0.01$ for both) in patients with critical compared with noncritical COVID-19, resulting in substantially higher prevalence of atherogenic dyslipidemia (46 vs. 24%, $P = 0.011$). Reported use of diuretics, ACE inhibitors, calcium channel blocker therapy, and lipid-lowering drugs was similar in both groups (data not shown), as well as in-hospital administration of hydroxychloroquine, antivirals, and tocilizumab (Table 1).

Factors Associated With Study Outcomes

In the univariate analysis, characteristics of patients prior to admission significantly associated with the primary outcome were age (OR 1.05 [95% CI 1.02–1.08], $P < 0.001$) and reported diagnosis of diabetes (OR 2.58 [95% CI 1.10–6.03], $P = 0.018$) (Table 2). Time from symptoms onset to hospitalization (OR 0.88 [95% CI 0.79–0.97], $P = 0.015$), as well as admission levels of CRP, IL-6, procalcitonin, D-dimer, 25-OH-vitamin D, fasting glucose, triglycerides, and HDL, were all significantly associated with worse outcome in the crude analysis ($P = 0.01$ for all) (Table 2). Detection of atherogenic dyslipidemia at admission was also associated with adverse COVID-19 outcome (OR 2.96 [95% CI 1.28–6.83], $P = 0.011$). The subsequent multivariable analysis, with further adjustment for age and sex, confirmed significant associations with poorer COVID-19 outcome for most of the variables that previously emerged in the crude analysis, except for the time to ER presentation and IL-6 and LDL levels (Table 2). Among the included comorbidities, presence of

Table 1—Main clinical characteristics at admission of the overall population (*N* = 118)

	All	Critical COVID-19 (*n* = 43)	Noncritical COVID-19 (*n* = 75)	*P**
Age (years)	68.1 ± 15.5	74.9 ± 11.1	64.2 ± 16.3	<0.001
Female sex	45 (38)	18 (41)	27 (36)	0.528
Time to ER admission (days)	5 (1–8)	2.5 (1–7)	6 (2.5–8.5)	0.013
BMI (kg/m^2)	24.5 ± 3.8	24.4 ± 4.1	24.5 ± 3.7	0.933
Serum CRP (mg/L)	85.2 (23.5–152)	123.7 (70.7–214.6)	57.2 (14.2–112.1)	<0.001
IL-6 (pg/mL)	31.9 (13.9–81.1)	66.7 (24.1–112)	26.5 (10.7–57.6)	0.009
TNF-α (pg/mL)	22.3 (9.14–38.1)	18.9 (7.8–23.7)	27.3 (10.4–48.2)	0.183
Procalcitonin (ng/mL)	0.09 (0.04–0.29)	0.17 (0.06–0.87)	0.06 (0.03–0.13)	0.001
D-dimer (mg/L)	0.92 (0.48–1.76)	1.58 (0.86–3.54)	0.71 (0.38–1.34)	<0.001
eGFR (mL/min)	82.7 ± 32.7	81.1 ± 38.3	83.4 ± 30.7	0.787
25-OH-vitamin D (nmol/L)	30.95 (15.60–46.17)	22.46 (11.85–34.44)	33.20 (22.21–57.41)	0.001
Total cholesterol (mmol/L)	3.78 ± 1.11	3.52 ± 1.08	3.93 ± 1.11	0.075
LDL (mmol/L)	2.25 ± 0.92	1.96 ± 0.94	2.39 ± 0.88	0.032
HDL (mmol/L)	0.82 ± 0.37	0.68 ± 0.25	0.90 ± 0.40	0.003
Triglycerides (mmol/L)	1.46 (1.04–1.85)	1.78 (1.41–2.70)	1.34 (0.98–1.71)	<0.001
Atherogenic dyslipidemia	38 (32)	20 (46)	18 (24)	0.011
Fasting glucose (mmol/L)	6.39 ± 3.17	7.38 ± 3.92	5.83 ± 2.51	0.012
HbA_{1c} (mmol/mol)	47 ± 13	44 ± 12	48 ± 13	0.529
Diabetes	30 (25)	16 (37)	14 (19)	0.026
Hypertension	52 (45)	18 (42)	34 (45)	0.882
Cardiovascular diseases	40 (34)	18 (44)	22 (29)	0.085
COPD	9 (7.8)	4 (9.8)	5 (6.7)	0.398
In-hospital therapy				
Tocilizumab	22 (18.4)	11 (25.0)	11 (14.9)	0.079
Antivirals	84 (71.3)	27 (63.4)	57 (75.7)	0.381
Hydroxychloroquine	106 (89.6)	33 (78)	73 (95.9)	0.205

Data are mean ± SD, median (interquartile range), or *n* (%). *Unpaired data, *t* test for continuous variables (skewed variables were log-transformed) or Fisher exact test for discrete traits.

diabetes (OR 1.70 [95% CI 1.05–4.32], $P = 0.023$) and atherogenic dyslipidemia (OR 2.53 [95% CI 1.13–6.32], $P = 0.018$), but not hypertension or presence of cardiovascular disease, were significantly related to the course of disease. Finally, in the sensitivity analysis with consideration of in-hospital death or admission to ICU as separate outcomes, atherogenic dyslipidemia was significantly related to in-hospital death (OR 3.63 [95% CI 1.24–5.77], $P = 0.009$), whereas the association with admission to ICU was not significant (OR 2.02 [95% CI 1.02–7.63], $P = 0.11$).

Atherogenic Dyslipidemia and Critical COVID-19

Multivariable analysis of factors associated with the composite outcome was repeated in a subgroup of patients with evidence of atherogenic dyslipidemia on admission (Table 3). In these patients, most of the associations seen in the overall population were not confirmed, with only admission levels of serum CRP, D-dimer, and triglycerides being significantly related with the in-hospital outcome. Among these variables, the strongest associations with adverse COVID-19 outcome were observed for CRP (OR 4.03 [95% CI 1.55–8.22], $P = 0.012$) and triglycerides levels (OR 2.62 [95% CI 1.26–4.13], $P = 0.005$). The analysis was repeated for isolate mortality, with evidence of significant relationship (OR 3.12 [95% CI 1.69–4.89], $P = 0.004$), whereas isolate admission to ICU was not associated (OR 1.22 [95% CI 0.99–1.52], $P = 0.23$). Finally, we tested the relationship between triglycerides levels and inflammatory markers associated with subsequent worse prognosis of COVID-19. Linear regression between triglycerides and CRP, D-dimer, and procalcitonin is plotted in Figs. 1, 2, and 3, respectively, with Spearman coefficients revealing significant positive associations in all the performed analysis ($P < 0.05$ for all). Similar results were seen in the subgroup with atherogenic dyslipidemia (not shown).

CONCLUSIONS

In the current study we report significant association between detection of atherogenic dyslipidemia at admission and subsequent adverse outcome of disease in patients hospitalized for COVID-19. More specifically, atherogenic dyslipidemia was strongly related to mortality, resulting in more than threefold increased probability of association with in-hospital death (OR 3.63 [95% CI 1.24–5.77]; $P = 0.009$). Triglycerides levels detected at admission were also positively associated with CRP, procalcitonin, and D-dimer levels, which in turn were higher in patients with critical COVID-19. F1-F3

Presence of high triglyceride levels is frequent in type 2 diabetes and closely

Table 2—Univariate and multivariate analysis of factors associated with in-hospital death or ICU admission for all individuals

	Univariate analysis, OR (95% CI)	*P*	Multivariate analysis, OR (95% CI)*	*P*
Age (years)	1.05 (1.02–1.08)	<0.001	1.06 (1.03–1.08)	<0.001
Male sex	1.28 (0.59–2.75)	0.520	1.65 (0.63–3.41)	0.240
Days to ER admission	0.88 (0.79–0.97)	0.015	0.91 (0.80–1.35)	0.142
BMI (kg/m^2)	0.99 (0.89–1.10)	0.956		
Serum CRP (mg/L)†	3.95 (1.66–9.40)	<0.001	3.04 (1.22–7.59)	0.017
IL-6 (pg/mL)†	3.82 (1.66–8.81)	0.002	1.65 (0.93–6.43)	0.114
TNF-α (pg/mL)†	0.36 (0.13–1.02)	0.569		
Procalcitonin (ng/mL)	1.94 (1.04–3.65)	0.038	1.77 (1.04–3.42)	0.032
D-dimer (mg/L)	1.89 (1.30–2.75)	<0.001	1.62 (1.10–2.37)	0.015
eGFR (mL/min)	0.99 (0.98–1.01)	0.784		
25-OH-vitamin D (nmol/L)	0.90 (0.84–0.97)	0.004	0.96 (0.87–0.98)	0.016
Total cholesterol (mmol/L)	0.70 (0.47–1.04)	0.079		
HDL (mmol/L)	0.10 (0.02–0.48)	0.005		
LDL (mmol/L)	0.56 (0.32–0.97)	0.037	0.65 (0.36–1.17)	0.140
Triglycerides (mmol/L)	3.96 (1.90–8.23)	<0.001	2.85 (1.81–8.17)	<0.001
Atherogenic dyslipidemia	2.96 (1.28–6.83)	0.011	2.53 (1.16–6.32)	0.018
Fasting glucose (mmol/L)	1.27 (1.08–1.51)	0.004	1.11 (1.02–1.43)	0.026
HbA_{1c} (mmol/mol)	0.97 (0.91–1.05)	0.526		
Diabetes	2.58 (1.10–6.03)	0.018	1.70 (1.05–4.32)	0.023
Hypertension	0.94 (0.44–2.03)	0.882		
Cardiovascular diseases	1.88 (0.85–4.16)	0.115		
COPD	1.51 (0.38–5.97)	0.551		

*Multivariate regression models including age and sex. †Log-transformed before analysis.

linked to insulin resistance (10,16). It is now established that patients with preexisting diabetes, especially if associated with obesity and other related comorbidities, are at high risk of death or prolonged and complicated hospitalization for COVID-19, as reported by several large retrospective studies from different geographic areas (2,4,5). In our smaller population, we confirmed presence of diabetes as major driver of severity of disease, with an overall prevalence of nearly 25%, which is not dissimilar from the age-standardized prevalence of diabetes reported in Italy (23). Interestingly, fasting glucose on admission (mmol/L), but not HbA_{1c} levels, turned out to be related to in-hospital death or intubation for respiratory distress (OR 1.11 [95% CI 1.02–1.43], $P = 0.026$). Such an association could be bidirectional. Indeed, hyperglycemia itself can directly affect host defense, including granulocyte and macrophage function (8), and amplify the hyperimmune response associated with severe COVID-19 (24). Alternatively, increased blood glucose could be the result of the metabolic stress determined by more severe infection. By contrast, HbA_{1c} levels were not dissimilar between patients with poorer or better outcomes, while prevalence of diabetes among patients was significantly higher for the groups with worse prognosis (37 vs. 19%, $P = 0.026$). These findings are not easy to interpret. According to hospital clinical records, no substantial differences emerged between patients with diabetes with critical and noncritical COVID-19 in terms of age, sex, and preadmission antihyperglycemic therapy. Particularly, routine insulin therapy prior to admission, which has been associated with mortality in another COVID-19 hospitalized cohort (25), was not dissimilar between groups in our population. Information about microvascular complications, which would have been useful to

Table 3—Analysis of factors associated with in-hospital death or ICU admission in individuals with atherogenic dyslipidemia (*n* = 38)

	OR*	95% CI	*P*
Serum CRP (mg/L)†	**4.03**	**1.55–8.22**	**0.012**
IL-6 (pg/mL)†	1.17	0.29–4.71	0.860
Procalcitonin (ng/mL)	1.79	0.68–2.11	0.144
D-dimer (mg/L)	**2.70**	**1.17–5.61**	**0.026**
25-OH-vitamin D (nmol/L)	0.97	0.94–1.01	0.074
LDL (mmol/L)	0.61	0.17–1.15	0.436
Triglycerides (mmol/L)	**2.62**	**1.26–4.13**	**0.005**
Fasting glucose (mmol/L)	1.16	0.95–1.38	0.141
Diabetes	1.37	0.35–3.19	0.666

Boldface indicates significance at $P < 0.05$. *Multivariate regression models including age and sex. †Log-transformed before analysis.

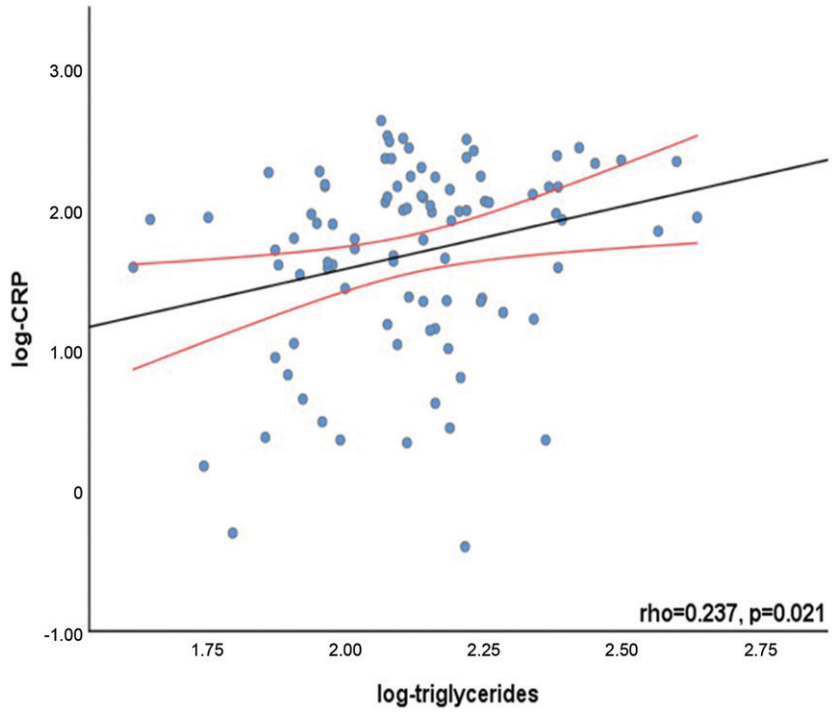

Figure 1—Regression analysis (Spearman) between serum triglycerides and C-reactive protein (CRP) levels at admission in the overall population (*N* = 118).

better define severity of diabetes, was unfortunately not available. Additionally, HbA_{1c} levels were generally very low, even in the group with higher mortality and intubation rates (44 ± 12 mmol/mol), reflecting preexisting optimal glycemic control for patients with diabetes. These unusual low levels of HbA_{1c} in our cohort could explain the lack of association with poorer in-hospital outcome of COVID-19.

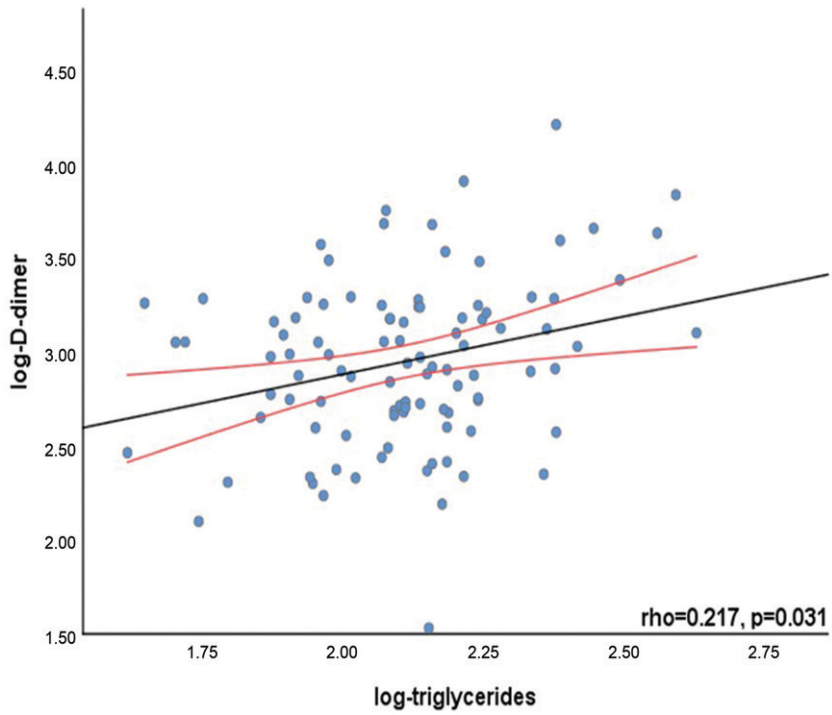

Figure 2—Regression analysis (Spearman) between serum triglycerides and D-dimer levels at admission in the overall population (*N* = 118).

Noteworthy, the lack of association between HbA_{1c} levels and mortality was recently confirmed in the 28-day follow-up analysis of the Coronavirus SARS-CoV-2 and Diabetes Outcomes (CORONADO) cohort, which included 2,796 subjects with diabetes hospitalized for COVID-19 in France (25). We believe, however, that understanding the role of glycemic control in severity of COVID-19 requires further investigations, given the number of observational studies in the general population (not hospitalized) reporting opposite results on the prognostic role of elevated HbA_{1c} for individuals with SARS-CoV-2 infection (26,27).

Beside diabetes, we found atherogenic dyslipidemia to be strongly and independently associated with the primary outcome of in-hospital death or admission to ICU (OR 2.53 [95% CI 1.16–6.32], $P = 0.018$). In addition, both triglycerides and HDL quantitative levels on admission were significantly impaired in patients with critical compared with noncritical disease ($P < 0.01$ for both), and triglycerides were significantly related to the primary outcome in the multivariable analysis (Table 2). Of note, these lipid abnormalities were above all related to in-hospital mortality, whereas the association with isolate admission to ICU was not significant. This result is likely attributable to the limited number ($n = 8$) of patients who required intubation and were discharged from the ICU thereafter, resulting in a definition of critical COVID-19 primarily including those patients who died with COVID-19. This is undoubtedly a pitfall of this cohort, which was burdened by a remarkable mortality rate of 29%, at least in part attributable to the limited knowledge of disease management at the very beginning of the outbreak in Italy. Accordingly, the in-hospital mortality rate observed in our population is not dissimilar from that of other reports during the ascending phase of the COVID-19 pandemic in Italy (3,28). In general, the in-hospital fatality rate reported in Italy was remarkably higher than in China or in Northern Europe (2,25) during the same period, and this means that findings obtained in a specific population might not be automatically extendable to different geographic regions and that the depiction of national cohorts might contribute to explaining this heterogeneity and to better stratification of patients.

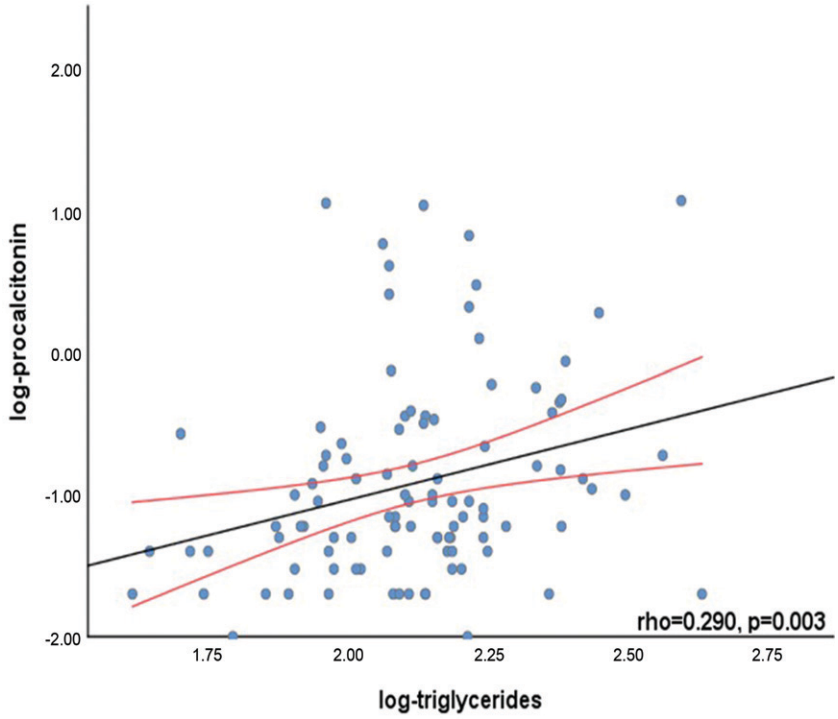

Figure 3—Regression analysis (Spearman) between serum triglycerides and procalcitonin levels at admission in the overall population (N = 118).

In looking at patients with atherogenic dyslipidemia, admission triglycerides levels were significantly associated with poor in-hospital outcome alongside serum CRP and D-dimer (Table 3) and positively correlated with serum CRP, D-dimer, and procalcitonin levels. We can speculate that these results may reflect the significance of insulin resistance in patients with critical COVID-19. High triglycerides and low HDL are together the more significant lipidic abnormalities attributable to insulin resistance (16) and are largely reported to be associated with systemic inflammation and vascular dysfunction, which are in turn dramatically enhanced in critical cases of COVID-19 (29,30). These findings are indirectly confirmed by a recent study showing that increased abdominal visceral adipose tissue, which is closely linked to insulin resistance and chronic inflammation, increases the risk of ICU admission for COVID-19, independently of BMI (31). Further confirmation of the role of insulin resistance in COVID-19 comes from the study of Ren et al. (32), who reported significant association of triglycerides and glucose index (TyG) with mortality and morbidity in COVID-19 patients. On the other hand, several lipid abnormalities have been reported in patients with a variety of different acute infectious diseases, including viral infections. Specifically, LDL and HDL cholesterol levels are frequently decreased and plasma triglycerides are elevated or inappropriately normal for the poor nutritional status (33), and these alterations in lipids generally correlate with severity of the underlying infection. The positive association of combined high triglycerides and low HDL levels with poorer outcome and mortality in severe COVID-19 patients could therefore be attributed to the role that insulin resistance and counterregulatory stress hormones exert in acute infectious diseases. Of note, in accordance with what we observed in our patients with COVID-19, low levels of serum HDL and high triglycerides have previously been associated with mortality and poor prognosis in patients with severe sepsis (34). In particular, the effect on triglycerides has been attributed to the increasing levels of multiple plasma cytokines (e.g., IL-1, IL-6, TNF-α) since the early stages of infection, affecting both hepatic VLDL production and clearance of triglyceride-rich lipoproteins (35). In this context, the cytokine storm described in COVID-19 patients might induce an immune-mediated dyslipidemia leading to reduced HDL and LDL, and increased triglyceride-rich lipoproteins (36). As shown in Table 2, the pattern of proatherogenic dyslipidemia and low LDL levels might correlate with poor prognosis in adults with severe COVID-19. However, given the retrospective nature of our analysis, we cannot be conclusive on this point, namely, whether lipid abnormalities observed in our patients are preexisting factors increasing the risk of severity of COVID-19 or, alternatively, are to be considered as biochemical derangements attributable to the cytokine storm occurring in the most critical cases.

Consistent with previous findings, older patients from our population study were more susceptible to poorer COVID-19 outcome ($P < 0.001$), as were those with higher levels of CRP, IL-6, procalcitonin, and D-dimer on admission ($P < 0.05$ for all). Conversely, neither hypertension nor cardiovascular disease were associated with critical COVID-19, which is in contrast with most previous reports (20,37,38), as well as for overweight/obesity. While not statistically significant ($P = 0.085$), more patients had cardiovascular diseases who died or were admitted to ICU, so we cannot definitively rule out a contribution of cardiovascular comorbidities as risk factors for adverse course of COVID-19 in our population. A larger sample study would have likely changed this estimation. The lack of association with overweight is probably attributable to the mean BMI value for this population, which was overall within the normal range (mean ± SD 24.5 ± 3.8 kg/m^2). Measurement of waist circumference would have been very useful to better address this point, but this is unfeasible in most patients admitted with severe pneumonia. We also found that hypertension was unrelated to adverse in-hospital course of COVID-19 in our cohort, in contrast with most (20,37,38), but not all (25), previous reports. Again, the limited sample size alongside the retrospective study design can be a drawback in such cases, and especially for hypertension, which was assessed only on an anamnestic basis and according to the list of ongoing medications at the time of admission, presenting a not negligible risk of misclassification. In addition, information on blood pressure control was not available, and this is another drawback of this analysis, since raised blood pressure has been associated with increased risk of dying from COVID-19, compared with well-controlled hypertension (39). For all these reasons, results from our study are not conclusive

on the association between hypertension and COVID-19.

The major limitation of this research is attributable to the retrospective data collection, at a single center, and to the lack of validation in an external cohort, which would have been useful for confirmation of both reproducibility and generalizability of results. Therefore, all statistics are deemed to be descriptive only. Second, also in light of complexity of the disease, the number of patients included is relatively small, implying some uncertainties in the estimated strength of the associations. However, these observations derive from a fully unselected population and thus should be easier to validate in potential future research involving larger populations. Third, fasting insulin levels would have been useful for a more precise estimation of insulin resistance and metabolic profile, but unfortunately plasma insulin is not routinely assessed when a patient is admitted to the ER. Finally, we recognize that our definition of atherogenic dyslipidemia is incomplete, since we lack measurements of apolipoprotein B and small-dense LDL, which are not commonly tested in routine practice. However, according to the objective and design of the current study, we believe that co-occurrence of high fasting triglycerides and low HDL levels can be considered as an acceptable, though incomplete, surrogate indicator of insulin resistance.

In conclusion, our study provides evidence for the first time that atherogenic dyslipidemia detected on admission, and in particular hypertriglyceridemia, may be another independent metabolic abnormality associated with adverse prognosis in patients hospitalized with COVID-19, which deserves to be further investigated in larger populations. Evaluation of lipid profile, alongside other already established risk factors, should therefore be encouraged in patients with severe COVID-19.

Funding. Funding for this work was provided by Progetti di ricerca di Rilevante Interesse Nazionale (PRIN) 2017 (no. 201793XZ5A_004), Fondazione Umberto Di Mario, and Fondazione Roma.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. A.B., A.A., and S.D.T. contributed to drafting of the manuscript. A.B., F.M.G., V.R., and M.R. contributed to analysis and interpretation of data. A.B., P.R., and D.L. contributed to study concept and design. A.A. contributed to statistical analysis. A.A., L.G., S.D.T., A.Mai., and I.D. contributed to acquisition of data. A.Mag., N.D.D., P.R., and D.L. contributed to critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript. A.B. and D.L. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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