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The impact of obesity and dyslipidemia on Remdesivir effectiveness in hospitalized patients with SARS-CoV-2-related pneumonia: An observational study

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Abstract *Background and aims:* Remdesivir (GS-5734), an inhibitor of the viral RNA-dependent, RNA polymerase was early identified as a promising therapeutic candidate against COVID-19. Our aim was to evaluate the impact of several metabolic parameters on Remdesivir effectiveness among hospitalized COVID-19 patients.

Methods and results: We conducted an observational study on patients with SARS-CoV-2-related pneumonia admitted between May 2020 and September 2021 to the COVID-19 Units of Internal Medicine, Pneumology and Intensive Care of Garibaldi Hospital, Catania, Italy, and treated with Remdesivir. The "Ordinal Scale For Clinical Improvement" was used to assess patients' clinical improvement within 28 days of hospitalization. Short-term mortality rate was also evaluated.

A total of 142 patients with SARS-CoV-2-related pneumonia were studied. The prevalence of obesity (20.7% vs. 41.9%, $p = 0.03$), the average BMI (27.1 ± 4.4 vs. 31.1 ± 6.1, $p < 0.01$) and the mean LDL-C levels (78 ± 19 mg/dl vs. 103 ± 18 mg/dl, $p = 0.03$) were significantly lower in early-improved (EI) compared to not-improved (NI) individuals. Obesity was negatively associated to clinical improvement after Remdesivir (OR 0.48, 95%CI 0.17–0.97, $p = 0.04$). Both obesity (OR 2.82, 95% CI 1.05–7.71, $p = 0.04$) and dyslipidemia (OR 2.78, 95%CI 1.17–7.16, $p = 0.03$) were significantly related to patients' mortality. Dyslipidemic subjects experienced a slower clinical improvement than non-dyslipidemic ones (Long-Rank $p = 0.04$).

Conclusion: Our study showed that unfavorable metabolic conditions such as obesity and dyslipidemia could predict a worse clinical response to Remdesivir as well as the mortality in hospitalized COVID-19 patients. Further prospective and larger-scale studies are needed to confirm these preliminary findings.

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1. Introduction

Since Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) disease (COVID-19) emerged at the end of 2019 in China, it rapidly became a global pandemic [1]. Clinical manifestations of COVID-19 usually range from asymptomatic state or mild infection to severe forms of the disease that are life threatening [2]. This ongoing outbreak has pushed the researchers' efforts to identify which clinical characteristics would have conferred to people an higher risk of getting infected, of developing critical illness and, ultimately, of dying from this disease [3]. On this regard, advanced age, male sex, the presence of chronic illness and/or multiple comorbidities (e.g. chronic lung diseases, cardiovascular diseases, obesity and diabetes mellitus) have been clearly identified as major risk factors for the development of severe COVID-19 [4–7]. Recent reports also indicated a role of dyslipidemia in severity and mortality from SARS-CoV-2 infection [8,9].

Several therapeutic agents have been investigated for clinical improvement and increasing survival of COVID-19 patients; some of them are anti-inflammatory drugs while the others including antivirals medications. Among antivirals, Remdesivir (GS-5734), an inhibitor of the viral RNA-dependent, RNA polymerase was identified early as a promising therapeutic candidate for this disease [10–12]. Food and Drug Administration (FDA) approved the use of Remdesivir in severe hospitalized COVID-19 patients under an emergency use authorization on May 1st, 2020. Afterward, on August 28th, 2020, authorization of Remdesivir administration was expanded to non-severe COVID-19 patients. Finally, on October 22nd, 2020, Remdesivir became the first drug with the FDA approval for the treatment of COVID-19 [13]. In Italy, the Italian Medicine Agency (AIFA) approved Remdesivir in patients with COVID-19 pneumonia on oxygen therapy not requiring high-flow oxygen or mechanical ventilation or extracorporeal membrane oxygenation (ECMO), and with symptom onset of less than 10 days.

Although the usefulness of this drug has been showed by several randomized controlled trials [10,12,14], there is still poor evidence regarding the clinical and biochemical predictors of Remdesivir effectiveness among patients hospitalized for SARS-CoV-2-related pneumonia.

Thus, the aim of the present study was to identify, in a real-world setting, any clinical condition and/or biochemical parameter able to predict an early clinical improvement (primary outcome) among Remdesivir-treated adult patients admitted to the hospital for SARS-CoV-2-related pneumonia.

2. Methods

We conducted a retrospective observational study on patients with SARS-CoV-2-related pneumonia, admitted between May 2020 and September 2021 to the COVID-19 Units of Internal Medicine, Pneumology and Intensive Care of Garibaldi Hospital, Catania, Italy. All the patients were treated with Remdesivir during the hospital stay.

The following baseline clinical, anthropometric and biochemical parameters were evaluated: body weight, height, body mass index (BMI, Kg/m^2), systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting plasma glucose (FPG), glycated hemoglobin (HbA1c, determined by high-performance liquid chromatography), total cholesterol, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C, calculated with Friedewald formula if triglycerides value was lower than 400 mg/dl [15]), triglycerides (TG), creatinine levels, estimated glomerular filtration rate (according to the Chronic Kidney Disease Epidemiology Collaboration formula [16]), glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), amylase, lipase, C-reactive protein (CRP), procalcitonin (PCT) and PaO_2/FiO_2 ratio.

The presence of different comorbidities was recorded and correlated to the clinical response to Remdesivir: hypertension (SBP $\geq$140 mmHg and/or DBP$\geq$ 90 mmHg, or taking antihypertensive medication), established cardiovascular diseases (myocardial infarction, heart failure, stroke), renal failure (eGFR $<$60 ml/min), diabetes mellitus (either anamnestic or newly diagnosed during the hospital stay), obesity (BMI $\geq$30 kg/m^2), dyslipidemia (defined according to the 2019 ESC/EAS guidelines cutoff values [17] or by already taking lipid-lowering drugs at the time of hospital admission), malignancies and chronic obstructive pulmonary diseases (COPD). Patients' smoking habit and concomitant medications were also recorded.

The previously validated "Ordinal Scale For Clinical Improvement" (OSCI) [12] was used to assess patients' early clinical improvement after Remdesivir (primary outcome), which was defined as the achievement of categories 1–3 on the scale and/or a 2-point reduction of the score (regardless of the starting level) within 28 days of hospitalization. The categories were as follows: 1, not hospitalized and no limitations of activities; 2, not hospitalized, with limitation of activities, home oxygen requirement, or both; 3, hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalization was extended for infection-control or other nonmedical reasons); 4, hospitalized, not requiring supplemental oxygen but requiring ongoing medical care (related to COVID-19 or to other medical conditions); 5, hospitalized, requiring any supplemental oxygen; 6, hospitalized, requiring noninvasive ventilation or use of high-flow oxygen devices; 7, hospitalized, receiving invasive mechanical ventilation or ECMO; and 8, death.

Patients were then defined as either early improved (EI) or not-improved (NI) on the basis of clinical achievements of the aforementioned criteria.

Secondary outcomes were the time to recovery, defined as the first day, during the 28 days after the first dose of Remdesivir, on which the patient met the above-mentioned criteria, and the short-term (within one month since hospital admission) mortality rate.

The study was conducted in compliance with the principles of the Declaration of Helsinki and its later amendments [18] and was approved by the local ethics committee.

3. Sample size and statistical analysis

We estimated that a sample size of 140 patients would have given at least 85% power to detect a difference of 30% in reaching the primary outcome (early clinical improvement after Remdesivir), with an alpha of 0.05. The effect size estimation was based on the rate ratio for recovery (1.29) of the main randomized controlled trial on Remdesivir efficacy, the Adaptive COVID-19 Treatment Trial (ACTT-1) [12].

Shapiro–Wilk and Kolmogorov–Smirnov tests were used to explore the distribution of continuous variables. Graphic analyses of histogram, Q–Q normality graph and asymmetry/standard error or kurtosis/standard error ratio supported the distribution of continuous variables exploration. EI and NI patients were compared by using Fisher exact test or χ^2 test when appropriate for categorical variables and by using Student's t test or Mann–Whitney test when appropriate for continuous variables. A two-sided p value < 0.05 was considered statistically significant.

A multivariate logistic regression model corrected by age, gender, smoking habit, available markers of inflammation (CRP, PCT) and concomitant therapy with Baricitinib, a Janus kinase (JAK) inhibitor, was used to quantify the odds ratios (OR) with 95% confidence interval (CI) for the primary outcome occurrence on the basis of the different comorbidities. Hosmer–Lemeshow post-estimation test was used to assess the model performance.

Moreover, linear regression was used to correlate continuous variables.

Finally, time to event (patients' clinical improvement according to OSCI) was assessed using the Kaplan–Meyer curves and compared between groups by the Long-rank test.

All the statistical analyses were performed using STATA 14.2 SE software (STATA Corp., College Station, Texas).

4. Results

A total of 248 COVID-19 patients were assessed for eligibility. Among them, 106 were excluded because they did not meet the criteria for starting therapy with Remdesivir (n = 72) or for the lack of information regarding primary outcome and/or mortality (n = 34). Thus, 142 patients treated with Remdesivir were retrospectively evaluated.

The baseline anamnestic and clinical characteristics of the studied population are summarized in Table 1. One hundred and eleven patients (EI, 78.2%) showed a clinical improvement at OSCI during the observational period.

As it was expected, EI patients were younger than NI ones (63.7 ± 13.0 vs. 74.3 ± 12.2, p < 0.01). The prevalence of obesity (20.7% vs. 41.9%, p = 0.03), the average BMI (27.1 ± 4.4 vs. 31.1 ± 6.1, p < 0.01) and the mean LDL-C levels (78 ± 19 mg/dl vs. 103 ± 18 mg/dl, p = 0.03) were significantly lower in EI compared to NI individuals (Table 2). No statistically significant differences were found in terms of concomitant medications at baseline for the treatment of patients' comorbidities in the two studied groups (Table 2).

Table 1 Baseline anamnestic and clinical characteristics of the studied population.

Patients' baseline characteristics (n = 142)	
Age (years)	66.0 ± 13.5
Males (n, %)	88 (61.9)
Smokers (n, %)	23 (16.2)
Obesity (n, %)	36 (25.3)
DM (n, %)	46 (32.4)
Hypertension (n, %)	97 (68.3)
Dyslipidemia (n, %)	37 (26.1)
ECD (n, %)	42 (29.6)
COPD (n, %)	18 (12.7)
Renal failure (n, %)	20 (14.1)
Malignancies (n, %)	15 (10.6)

Data are presented as means ± standard deviations (SD) for continuous variables or numbers and percentages (%) for categorical variables.
Abbreviations: DM, diabetes mellitus; ECD, established cardiovascular disease; COPD, chronic obstructive pulmonary diseases.

Among other comorbidities, obesity was negatively associated to clinical improvement after Remdesivir (OR 0.48, 95%CI 0.17–0.97, p = 0.04) (Table 3). Furthermore, both obesity (OR 2.82, 95% CI 1.05–7.71, p = 0.04) and dyslipidemia (OR 2.78, 95%CI 1.17–7.16, p = 0.03) were significantly related to early patient mortality (Table 4).

All the studied individuals underwent steroid therapy during hospitalization, while a similar percentage of patients in the two study groups was also treated with Baricitinib: 28.8% (32/111) vs. 25.8% (8/31) in EI vs. NI patients, respectively (p = 0.74).

Since Remdesivir response could be affected by the precocity of drug administration and by the patients' clinical status (in terms of respiratory performance) at the time of prescription [19], we assessed these parameters in our cohort according to both dyslipidemia and obesity status. Notably, the mean time for Remdesivir prescription (from the onset of symptoms) was not different in dyslipidemic vs. non-dyslipidemic (4.9 ± 1.5 days vs. 4.7 ± 1.9 days, respectively, p = 0.72) as well as in obese vs. non-obese (5.2 ± 2.0 days vs. 4.8 ± 1.8 days, respectively, p = 0.42) individuals. Moreover, average PaO_2/FiO_2 ratio at the time of first Remdesivir administration was similar in dyslipidemic vs. non-dyslipidemic (305.6 ± 107.9 vs. 321.1 ± 100.1, respectively, p = 0.49) and in obese vs. non-obese (315.2 ± 99.5 vs. 301.6 ± 97.5, respectively, p = 0.53) patients.

A linear correlation between BMI values and the number o days needed for clinical improvement was also found (Fig. 1). Thus, the higher was BMI in our cohort, the longer was the time needed for the patient to recover. Finally, dyslipidemic subjects experienced a slower clinical improvement than non-dyslipidemic ones (Long-rank p = 0.04) (Fig. 2). This clinical pattern was not evident among obese patients (Long-Rank p = 0.25) (Fig. 3).

No other statistically significant differences were found in our cohort.

Table 2 Clinical, anthropometrical and biochemical characteristics of post-Remdesivir early improved (EI) vs. not improved (NI) individuals at baseline.

Patients' characteristics	EI (n = 111)	NI (n = 31)	p
Demographic and anthropometrical			
Age (years)	63.7 ± 13.0	74.3 ± 12.2	**< 0.01**
Males (n, %)	71 (64.0)	17 (54.8)	0.35
BMI (Kg/m^2)	27.1 ± 4.4	31.1 ± 6.1	**< 0.01**
Smokers (n, %)	16 (14.4)	7 (22.5)	0.31
Comorbidities			
Obesity (n, %)	23 (20.7)	13 (41.9)	**0.03**
Hypertension (n, %)	74 (66.7)	23 (74.2)	0.43
Dyslipidemia (n, %)	26 (23.4)	11 (35.5)	0.26
DM (n, %)	33 (29.7)	13 (41.9)	0.19
ECD (n, %)	32 (28.8)	10 (32.2)	0.73
COPD (n, %)	12 (10.8)	6 (19.3)	0.21
Malignancies (n, %)	11 (9.9)	4 (12.9)	0.43
Renal failure (n, %)	14 (12.6)	6 (19.3)	0.34
Clinical and biochemical parameters			
FPG (mg/dl)	115 ± 21	119 ± 23	0.76
HbA1c (%)	6.3 ± 0.9	6.6 ± 1.2	0.67
Average SBP (mmHg)	135 ± 6.3	137 ± 8.3	0.56
Average DBP (mmHg)	85 ± 3.2	86 ± 2.9	0.77
Total Cholesterol (mg/dl)	142 ± 38	173 ± 34	0.11
HDL-C (mg/dl)	39 ± 13	42 ± 8	0.23
LDL-C (mg/dl)	78 ± 19	103 ± 18	**0.03**
Triglycerides (mg/dl)	122 ± 36	141 ± 33	0.29
Creatinine (mg/dl)	1.2 ± 0.6	1.3 ± 0.5	0.56
GOT (mg/dl)	35 ± 20	39 ± 25	0.40
GPT (mg/dl)	36 ± 29	31 ± 19	0.30
Amylase (U.I./l)	71 ± 35	71 ± 41	0.99
Lipase (U.I./l)	42 ± 26	46 ± 45	0.80
CRP (mg/l)	99 ± 48	126 ± 67	0.71
PCT (ng/ml)	0.1 ± 0.3	0.1 ± 0.2	0.82
PaO_2/FiO_2 ratio	310.6 ± 103.7	313.3 ± 95.9	0.68
Concomitant medications			
ARBs (n, %)	25 (22.5)	8 (25.8)	0.70
ACE-I (n, %)	26 (23.4)	8 (25.8)	0.78
Beta blockers (n, %)	15 (13.5)	5 (16.1)	0.71
CCB (n, %)	17 (15.3)	6 (19.3)	0.59
Aspirin (n, %)	60 (54.0)	17 (54.8)	0.93
Statins (n, %)	20 (18.0)	9 (29.0)	0.18
Ezetimibe (n, %)	5 (4.5)	2 (6.4)	0.66
Fibrates (n, %)	4 (3.6)	2 (6.4)	0.49
Insulin therapy (n, %)	10 (9.0)	6 (19.3)	0.11
Metformin (n, %)	28 (25.2)	7 (22.6)	0.76

Data are presented as means ± standard deviations (SD) for continuous variables or numbers and percentages (%) for categorical variables.

Abbreviations: EI, early improved patients; NI, not improved patients; BMI, body mass index; DM, diabetes mellitus; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; ECD, established cardiovascular disease; COPD, chronic obstructive pulmonary diseases; GOT glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; CRP, C-reactive protein; PCT, procalcitonin; ARBs, angiotensin II receptor blockers; ACE-I, angiotensin-converting enzyme inhibitors; CCB, calcium channel blockers.

5. Discussion

This study showed, for the first time to our knowledge, that unfavorable metabolic conditions such as obesity and dyslipidemia could predict not only (as it is already known) the severity of clinical course and mortality among SARS-CoV-2-infected individuals, but also worse clinical outcomes following Remdesivir in patients who are hospitalized for moderate-to-severe disease. In our population, in fact, obesity was negatively associated to clinical improvement after the antiviral therapy and (together with dyslipidemia) positively related to patients' mortality. Dyslipidemia affected also the rapidity of clinical response, being dyslipidemic subjects slower than non-dyslipidemic ones in improving their clinical condition.

Since COVID-19 developed and became a pandemic, it has been well established that the presence of several comorbidities such as obesity and dyslipidemia represent a risk factor of clinical severity for subjects affected by SARS-CoV-2 infection [8,20–25]. Even if the exact underlined mechanisms of these associations have not been uniquely established, it is believed that the main pathophysiological link between SARS-CoV-2 infection and the above-mentioned disorders resides in the aberrant immune response, which characterizes these morbid conditions [26]. COVID-19, in fact, usually encompasses three main phases. In phase 1, the virus binds with ACE2 receptor on alveolar macrophages and epithelial cells, triggering toll like receptor (TLR) mediated nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) signaling. This phenomenon reduces the early immune response and, ultimately, allows unchecked viral replication. Phase 2 is characterized by hypoxia and innate immunity mediated pneumocyte damage as well as capillary leak. Phase 3 is the so-called "cytokine storm", which is characterized by an abnormal and dysregulated immune response causing multi-organ inflammation, worsening respiratory symptoms and determining hemodynamic instability [27].

In detail, the association between COVID-19-related poor prognosis and the obesity state can be explained by the implication of several biological and physiopathological reasons. Firstly, it has been demonstrated that obesity violates the well-balanced system of adipocytes and immune cells, with subsequent disturbance to the immune surveillance system [28]. Immune system cells and adipocytes exhibit, in fact, similarities in structure and functions such as the production of various mediators, which could exert their action both locally and systemically. In obesity, macronutrient excess stimulates adipocytes to release pro-inflammatory cytokines such as tumor necrosis factor α (TNF-α), interleukin 6 (IL-6) and CRP as well as pro-thrombotic mediators such as fibrinogen and D-dimer [29,30]. Conversely, the production of anti-inflammatory adipocytokines (e.g. adiponectin) is reduced, thus predisposing the individual to a pro-inflammatory and pro-thrombotic state and to oxidative stress [31,32]. Furthermore, it is known that obesity itself can be responsible for an impaired immune response and altered chemotaxis and macrophage differentiation with an overall negative impact on the efficiency of defenses against pathogens [33]. Secondly, the well-known association of obesity with reduced lung function, impaired respiratory physiology

Table 3 Probability (odds ratios with 95% confidence interval) of patients' clinical improvement on the basis of the presence of the different comorbidities.

Patients' comorbidities	OR	p
Obesity	**0.48 (0.17–0.97)**	**0.04**
DM	0.65 (0.27–1.51)	0.30
Hypertension	1.52 (0.54–4.41)	0.41
Dyslipidemia	0.71 (0.26–1.18)	0.21
ECD	1.16 (0.75–1.75)	0.44
COPD	0.70 (0.22–2.08)	0.52
Renal failure	0.73 (0.25–2.24)	0.62
Malignancies	1.61 (0.39–6.87)	0.49

A multivariate logistic regression model corrected by: age, gender, smoking habit, available markers of inflammation (C-reactive protein, procalcitonin) and concomitant therapy with Baricitinib, was used to quantify the odds ratios (OR) with 95% confidence interval (CI) for the primary outcome to occur on the basis of the different comorbidities.
Abbreviations: DM, diabetes mellitus; ECD, established cardiovascular disease; COPD, chronic obstructive pulmonary diseases.

and poor response to mechanical ventilation places people who are overweight or obese at risk of severe illness and mortality from COVID-19 [34]. Thirdly, the overexpression in adipose tissue of the extracellular domain of angiotensin-converting enzyme-2 (ACE2), which is an enzyme that has been identified as a receptor for the spike protein of SARS-CoV-2, may also play a role in the pathophysiology of the obesity-related COVID-19 severity [35,36].

On the other hand dyslipidemia itself (which is commonly but not always related to overweight/obesity) could further complicate this condition of low-level inflammatory exposure and aberrant immune response. Accumulated lipids, particularly LDLs, are subject to oxidation, and oxidized LDLs lead to several downstream consequences such as a cytokine storm [37]. Oxidized LDL-C is also a powerful stimulator that can activate endothelial cells and monocytes, so it can increase the expression of a variety of inflammatory proteins and receptors and induce endothelial cell apoptosis through the NF-kB and caspases signaling, thus increasing monocyte levels, platelet activation, and vascular smooth muscle cell migration [38].

Table 4 Odds of dying within 30 days from hospital admission on the basis of the presence of the different comorbidities.

Patients' comorbidities	OR	p
Obesity	**2.82 (1.05–7.71)**	**0.04**
DM	1.50 (0.55–3.91)	0.42
Hypertension	1.30 (0.41–4.44)	0.65
Dyslipidemia	**2.78 (1.17–7.16)**	**0.03**
ECD	0.85 (0.51–1.42)	0.50
COPD	1.05 (0.26–3.60)	0.89
Renal failure	1.56 (0.50–5.29)	0.40
Malignancies	1.10 (0.24–4.67)	0.88

A multivariate logistic regression model corrected by: age, gender, smoking habit, available markers of inflammation (C-reactive protein, procalcitonin) and concomitant therapy with Baricitinib, was used to quantify the odds (OR) with 95% confidence interval (CI) of dying within 30 days from hospital admission on the basis of the presence of the different comorbidities.
Abbreviations: DM, diabetes mellitus; ECD, established cardiovascular disease; COPD, chronic obstructive pulmonary diseases.

Endothelial dysfunction could, indeed, have a central role in the association between dyslipidemia/obesity and worse prognosis among COVID-19 patients. Since COVID-19 is widely considered an endothelial disease [39,40] and both dyslipidemia and obesity are pre-existing conditions, which are known to induce endothelial dysfunction, it is likely that both of them (either additionally or synergistically) may worsen the endothelial response to infection.

That said, it is important to underline that in our cohort the disease was identified and treated precociously (less than 10 days since symptoms onset) by means of Remdesivir together with standard anti-inflammatory therapy. Nevertheless, both obese and dyslipidemic individuals showed significantly worse outcomes in terms of clinical improvement, time to recovery and mortality. This phenomenon might have an important biological meaning. It is possible to hypothesize, in fact, that metabolic dysfunctions could have played a deeper role in the pathophysiology of COVID-19 progression than previously thought, not only by affecting the "cytokine storm phase" (and therefore determining a dysregulation of patients' immune response), but also by interfering with the antireplicative effect of an antiviral drug (e.g. Remdesivir) already from the first phases of the disease (that is before the cytokine storm occurrence). Our study suggests, therefore, that treating and preventing obesity and dyslipidemia during pandemic could have a central role not only by decreasing inflammation-related infection severity, but also by ameliorating patients' response to antivirals during the very early stages of the disease. The latter consideration appears to be clinically crucial considering the importance of an early diagnosis and treatment on COVID-19-related outcomes.

This study has strengths and limitation. Among strengths both the real-world approach and the novelty of the topic should be mentioned. Main limitations are represented by the retrospective design of the study (whose conclusions need to be supported by further and adequately powered prospective clinical studies), by the lack of a control group of Remdesivir-untreated COVID-19 patients, which would have been critical to support our hypotheses, and by the lack of information on several inflammation mediators (e.g. IL-6, TNF-α, etc) and on the SARS-CoV-2 viral load. Another limitation regards the timing of lipid profile assessment. It is, in fact, known that circulating levels of total cholesterol and LDL-C are lowered during acute infections [41,42]. Since, in our study, dyslipidemia has been defined based on either concomitant therapy with lipid-lowering drugs or serum LDL-C levels at hospital admission, the detected percentage of dyslipidemic patients could have been underestimated.

Nevertheless, we believe that this paper offers useful insights regarding the impact of metabolic disorders on the prognosis of COVID-19 individuals in a specific clinical

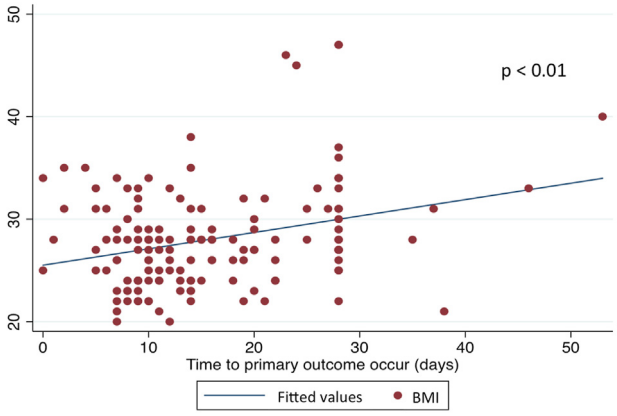

Figure 1 Linear correlation between BMI values and the number o days needed for clinical improvement after Remdesivir.

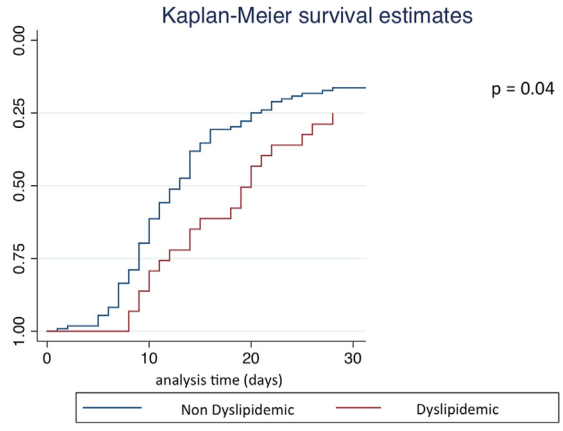

Figure 2 Kaplan–Meier survival estimates and Long-rank test in dyslipidemic and non-dyslipidemic subjects in terms of time to clinical improvement.

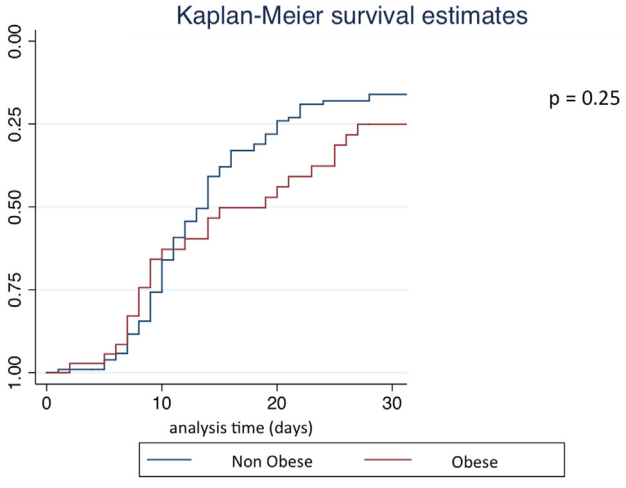

Figure 3 Kaplan–Meier survival estimates and Long-rank test in obese and non-obese subjects in terms of time to clinical improvement.

setting, which is represented by those hospitalized inpatients treated with Remdesivir.

Further larger-scale prospective studies are, however, needed to confirm our preliminary findings and to identify any additional predictors of differential clinical response to Remdesivir in SARS-CoV-2-infected patients.

Author contributions

Conceptualization, Andrea Tumminia, Raffaella Romano, Giuseppe Brugaletta, Roberto Scicali, Giuseppina Biondi, Rosario Oliveri, Marcello Romano, Paola Magnano San Lio; Resources, Andrea Tumminia, Raffaella Romano, Giuseppe Brugaletta, Giuseppina Biondi, Rosario Oliveri; Original Draft Preparation, Andrea Tumminia, Roberto Scicali; Review and Editing, Andrea Tumminia, Marcello Romano, Paola Magnano San Lio.

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Declaration of competing interest

All the authors declare no conflict of interest in connection with submitted material.

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