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COVID-19 induces proatherogenic alterations in moderate to severe non-comorbid patients: A single-center observational study

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ABSTRACT

Patients with COVID-19 can be asymptomatic or present mild to severe symptoms, leading to respiratory and cardiovascular complications and death. Type 2 diabetes mellitus (T2DM) and obesity are considered risk factors for COVID-19 poor prognosis. In parallel, COVID-19 severe patients exhibit dyslipidemia and alterations in neutrophil to lymphocyte ratio (NLR) associated with disease severity and mortality. To investigate whether such alterations are caused by the infection or results from preexisting comorbidities, this work analyzed dyslipidemia and the hemogram profile of COVID-19 patients according to the severity and compared with patients without T2DM or obesity comorbidities. Dyslipidemia, with a marked decrease in HDL levels, and increased NLR accompanied the disease severity, even in non-T2DM and non-obese patients, indicating that COVID-19 causes the observed alterations. Because decreased hemoglobin is involved in COVID-19 severity, and hemoglobin concentration is associated with metabolic diseases, the erythrogram of patients was also evaluated. We verified a drop in hemoglobin and erythrocyte number in severe patients, independently of T2DM and obesity, which may explain in part the need for artificial ventilation in severe cases. Thus, the control of such parameters (especially HDL levels, NLR, and hemoglobin concentration) could be a good strategy to prevent COVID-19 complications and death.

1. Introduction

The new coronavirus SARS-CoV-2, which triggers infections varying from asymptomatic to severe cases, has infected more than 173 million people worldwide, causing around 3.7 million deaths. It is responsible for the COVID-19 pandemic which reached almost all countries in less than 10 months and continues to cause a global strong impact on health systems due to a large number of affected people, the severity of the disease, and the associated long-term health sequelae [1]. Risk factors for COVID-19 poor prognosis include the presence of comorbidities such as obesity, type 2 diabetes mellitus (T2DM) [2], hypertension, and heart disease [3]. However, an expressive number of deaths were also observed for non-comorbid patients [4].

Dyslipidemia has long been established as an important risk factor for cardiovascular diseases (CVDs), associated with the development of atherosclerosis, myocardial infarction, and stroke [5]. The dyslipidemic profile involves increased triglycerides, decreased high-density lipoprotein (HDL) levels, and abnormal low-density lipoprotein (LDL) composition and all these components have been shown to be atherogenic [6]. Furthermore, lower levels of HDL are associated with the worst clinical outcomes in patients with community-acquired pneumonia [7] and with increased neutrophil to lymphocyte ratio (NLR) in patients with coronary artery disease [8]. Dyslipidemia has also been associated with severe outcomes of COVID-19 patients [5] where low

Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides; VLDL, very-low-density lipoprotein; T2DM, Type 2 diabetes mellitus; CVDs, cardiovascular diseases; ICU, Intensive Care Units; RT-PCR, real-time reverse transcription-polymerase chain reaction; BMI, Body Mass Index.

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levels of total cholesterol (TC), HDL, and LDL were correlated with disease severity and mortality [9]. On the other hand, it is known that patients with type 2 diabetes mellitus (T2DM) and obesity often exhibit dyslipidemia [10,11]. Likewise, the NLR has been associated with systemic inflammation [12] and it is significantly increased in prediabetic and diabetic patients [13]. Hemoglobin concentration is another predictor for metabolic syndrome [14,15], which includes dyslipidemia, T2DM, and obesity.

Thus, in this work, we aimed to verify if the pre-existence of T2DM or obesity would account for COVID-19-induced serum alterations correlated with worse outcomes. We analyzed the lipid, NLR, and erythrogram profiles of consecutive recruited COVID-19 patients according to the severity of the disease and compared them to the data excluding T2DM or obese patients. Because comorbidities are not always related to COVID-19 severity and death, we hypothesized that, besides the well-known inflammatory profile, COVID-19 would be causing serum alterations observed in metabolic syndromes and hence contributing to worsening of symptoms and death. The understanding of metabolic factors as predictors for the outcomes of SARS-CoV-2 infection may enable an accurate intervention prior to the severity establishment and it could be used as an alert to improve or even anticipate the treatment strategy.

2. Methods

2.1. Study design, description, and participants

This retrospective, observational, single-center study was approved by the Local Research Ethics Committee (No. CAAE: 32443020.4.0000.5501). The participants signed a Free and Informed Consent form, after detailed explanations about the purpose and methodology of the research. All consecutive patients with COVID-19 admitted to the Municipal Hospital of Taubate (Brazil) from May 18th to September 9th, 2020, were included in this study.

The single-center study was composed of 93 SARS-CoV-2 positive patients confirmed using RT-PCR test performed from nasopharyngeal swab samples, and 14 patients with a negative test, which comprised the control group. Six patients who reported dyslipidemia as an underlying medical condition were excluded from the study. The COVID-19 patients were classified according to the severity of the disease and divided into three subgroups, according to the Guidelines of the Brazilian Ministry of Health [16]. Detailing of groups and characteristics are listed in Table 1, which include age, body mass index (BMI), gender, the difference in days between the onset of symptoms and blood collection (Δ symptoms/blood collection), the difference in days between hospital admission and blood collection (Δ hospital admission/blood collection) for G2 and G3 groups, and the comorbidities reported.

2.2. Comorbidities parameters

Obesity was considered as BMI $\geq$ 30 [17]. Report data was described according to STROBE Statement [18]. Diabetes mellitus was diagnosed according to the standards of the American Diabetes Association and Brazilian Ministry of Health [19], which were briefly described as fasting plasma glucose (at least 8 h) level $\geq$ 7.0 mmol/L (126 mg/dL), or 2 h plasma glucose level $>$ 11.1 mmol/L (200 mg/dL) or random plasma glucose level $\geq$ 200 mg/dL with classic symptoms of DM, as polyuria, polydipsia, and unexplained weight loss.

2.3. Clinical laboratory procedures

Blood samples from G1 patients were collected during infection within 6–7 days after symptoms onset. The blood collection for G2 and G3 groups was performed during the hospitalization period (before COVID-19 resolution). The hemogram and levels of total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and very-low-density lipoprotein (VLDL) cholesterol were analyzed in the serum of patients. Tests were carried out at the clinical laboratory ClinicaLab (Barueri, Brazil) certified by the Excellence Program for Medical Laboratories of Brazilian Society of Clinical Pathology, following the guidelines of the Dyslipidemias and Atherosclerosis Prevention of the Brazilian Society of Cardiology.

2.4. Statistical analysis

Statistical analysis was performed using GraphPad Prism software. The data presented in the table were analyzed using the Chi-square test, One-Way ANOVA, or *t*-test according to data variables. All quantitative graphic data were tested for normality using the D'Agostino & Pearson test. Upon normality of data, One-Way ANOVA followed by Tukey's or Holm-Sidak's multiple comparisons test was used. When data were not parametric, the Kruskal-Wallis test followed by Dunn's multiple comparison test was employed. For comparisons between two groups, unpaired *t*-test (for parametric data) or Mann-Whitney test (for non-parametric data) were employed. Statistical differences were assumed considering $p < 0.05$.

3. Results

3.1. Characteristics and pre-comorbidities of patients according to illness severity

The characteristics of the participants (Table 1) showed that age is significantly correlated with the disease severity; as expected, older adults are predominant in G3 compared to G1. There was also a

Table 1
Groups and participants characteristics.

Characteristics	Participants with negative RT-PCR test	COVID-19 patients were designed for each group according to the severity			
Category, (participants)	Control group (14)	Group - mild (12)	Group 2 - moderate (49)	Group 3 - severe (32)	p
Age	43.8 ± 11.6	38.4 ± 8	55.5 ± 18.0	62.8 ± 14.9	***
Gender:					ns
Male	29% (4)	33% (4)	59% (29)	59% (19)	
Female	71% (10)	67% (8)	41% (20)	41% (13)	
Δ symptoms/blood collection (days)		4.3 ± 2.3	12.2 ± 3.9	14.1 ± 9.3	***
Δ hospital admission/blood collection (days)			5.3 ± 5.7	8.1 ± 6.3	*
Investigated comorbidities:					
Obesity	29% (4)	25% (3)	47% (23)	22% (7)	ns
T2DM	14% (2)	8% (1)	27% (13)	44% (14)	ns
Clinical criteria for group division		**Home isolation**	**Admitted to the inpatient unit**	**Admission to the ICU**	

Data were represented as the media ± SD or the percentage of individuals followed by the corresponding raw number (n). p values were calculated using the Chi-square test, One-Way ANOVA, or *t*-test according to data variables. *** $p < 0.001$, ** $p < 0.01$ and * $p < 0.05$ indicates a statistically significant difference amongst groups.

difference amongst G1, G2, and G3 groups in the interval (days) from the onset of symptoms to the collection of blood, and the hospital admission and blood collection (for G2 and G3 groups).

No differences were observed in gender and BMI amongst participants. The information related to pre-existing comorbidities (Table 1) revealed a higher incidence of T2DM in patients from G2 and G3, upon which the disease manifested more severely, compared to G1 and control groups.

3.2. Non-T2DM and non-obese COVID-19 patients exhibit dyslipidemia in moderate to severe cases

Because T2DM and obesity can induce sustained modifications in the serum lipid levels of patients [10,11], we analyzed whether these conditions would be responsible for the lipid alterations already observed in COVID-19 patients [20]. First, we examined the lipid profile of all patients and control individuals recruited in this study, and, in accordance with Literature [9], our data show that alterations in lipid serum factors follow the severity of COVID-19. Triglycerides of patients belonging to both G2 ($p = 0.0018$) and G3 ($p = 0.0084$) were increased when compared to the patients from the control group (Fig. 1A). Likewise, such an increase was also verified for non-T2DM (Fig. 1B) and non-obese (Fig. 1C) G2 and G3 patients. VLDL cholesterol was also significantly increased in both G2 and G3 groups compared to control individuals ($p = 0.0145$ and $p = 0.0234$, respectively) (Fig. 1D). Similarly, non-T2DM (Fig. 1E) and non-obese (Fig. 1F) G2 and G3 patients presented increased VLDL levels when compared to control individuals. HDL cholesterol exhibited the most significant alterations observed amongst groups ($F_{3, 103} = 24.57$), in which the mean of HDL levels from both G2 and G3 groups were below the reference values and decreased in relation to both controls ($p < 0.0001$ for G2 and G3) and G1 groups ($p = 0.0009$ and $p = 0.007$ for G2 and G3, respectively) (Fig. 1G). Such data was also verified for non-T2DM (Fig. 1H) and non-obese (Fig. 1I) G2 and G3 COVID-19 patients. Finally, total cholesterol and LDL levels were decreased in the G3 group compared respectively to control subjects or to all groups (Supplementary Fig. 1A, D). Total cholesterol was also decreased in non-T2DM and non-obese G3 patients (Supplemental Fig. 1B, C) as well as LDL levels of non-T2DM when compared to patients belonging to G1 (Supplemental Fig. 1E). When excluding non-obese patients, no differences were observed in LDL levels of patients (Supplemental Fig. 1F). Importantly, no differences were observed in increased TG and VLDL and decreased HDL levels between T2DM and

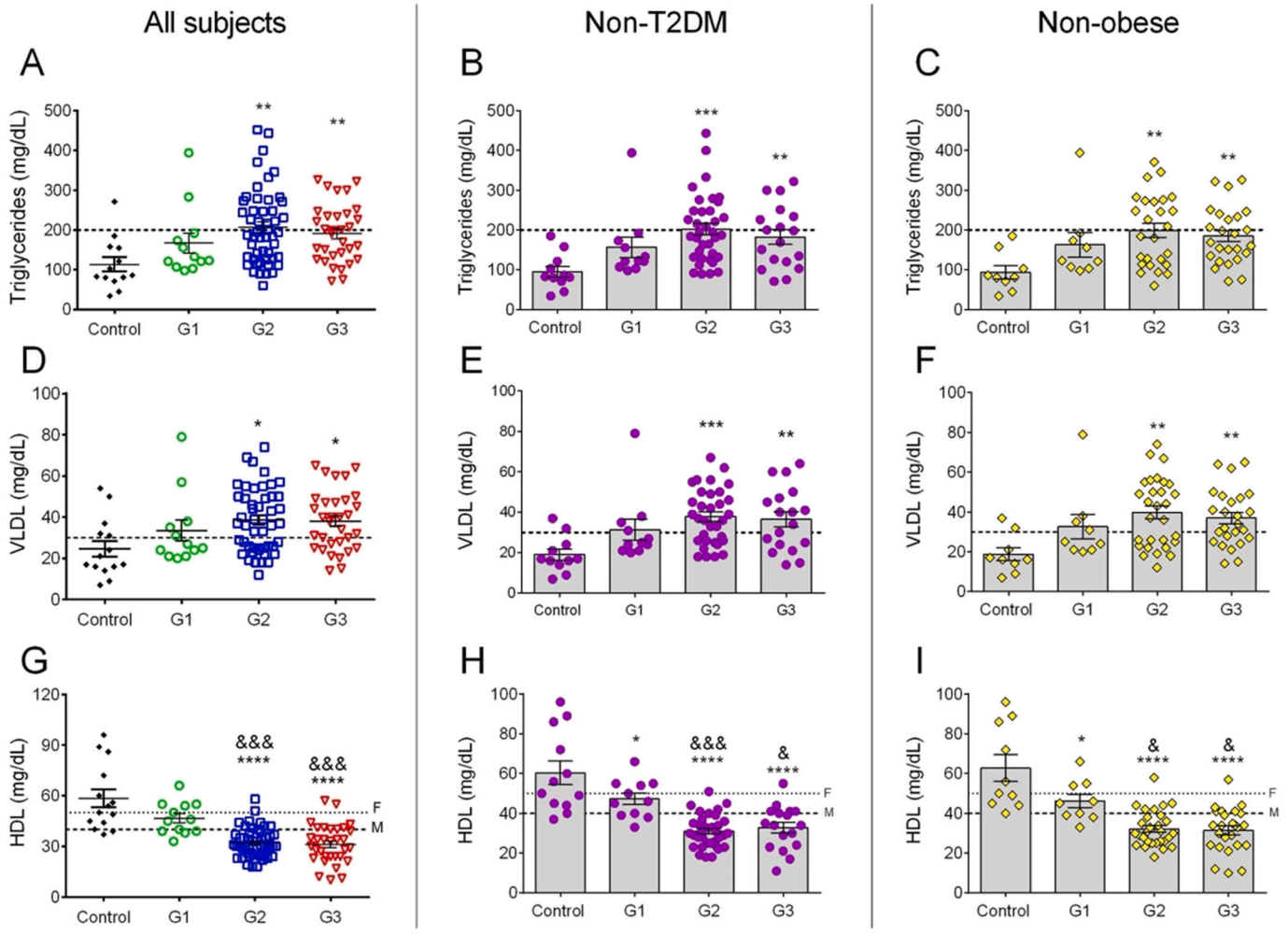

Fig. 1. Lipid serum profile according to the severity of the disease observed in COVID-19 patients with or without comorbidities. Serum from COVID-19 patients divided according to severity (G1: Group 1 – mild; G2: Group 2 – moderate, and G3: Group 3 – severe) or control individuals (Control) was obtained and used to quantify triglycerides (A–C), VLDL (D–F), and HDL (G–I) levels of all patients (A, D, G) and of non-T2DM (B, E, H in purple) and non-obese (C, F, I in yellow) individuals. Dashed lines indicate the upper limit for TG, and VLDL, and the lower limit for HDL, this last one being different for male (M) and female (F) individuals. Kruskal-Wallis test followed by Dunn's multiple comparison test for A–F, and ordinary one-way ANOVA followed by Tukey's test for G–I. *$p < 0.05$ compared to control group (**$p < 0.01$, ***$p < 0.001$, and ****$p < 0.0001$); &$p < 0.05$ compared to G1 (&&$p < 0.01$, and &&&$p < 0.001$). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

non-T2DM, and obese and non-obese patients from both G2 and G3 (Supplemental Fig. 2A–F).

3.3. Non-T2DM and non-obese COVID-19 patients exhibit increased neutrophil to lymphocyte ratio in moderate to severe cases

Increased NLR is associated with the severity of metabolic diseases such as T2DM and obesity [21]. On the other hand, NLR has been considered as a risk factor for mortality in hospitalized COVID-19 patients [22,23]. In addition, NLR has been considered an important parameter of systemic inflammation for different conditions [24–27].

Thus, we next evaluated hemogram parameters and the NLR of COVID-19 patients amongst groups, and also of patients without T2DM or obesity to verify if increased NLR would be a consequence of comorbidities. As expected, neutrophilia was observed in patients from both G2 and G3 groups when compared to individuals included in the control group ($p = 0.0053$ and $p < 0.0001$, respectively) and in G1 group ($p = 0.0197$ and $p = 0.0004$, respectively) (Fig. 2A). Such increase in neutrophils number was also found in non-T2DM (Fig. 2B) and non-obese (Fig. 2C) patients from G2 and G3 groups. Lymphocytes were decreased in G2 patients when compared to control ($p = 0.0327$) and G1 ($p = 0.0238$) individuals, and in G3 when compared to control, G1 ($p < 0.0001$), and G2 ($p = 0.0443$) (Fig. 2D). Similarly, non-T2DM G2 and G3 patients also exhibited a decrease in lymphocytes number (Fig. 2E) whereas only non-obese G3 patients presented a significant decrease in lymphocyte number when compared to control and G1 individuals (Fig. 2F). As expected, NLR followed COVID-19 severity which was increased in individuals from G2 ($p = 0.0013$ and $p = 0.002$ compared to control and G1 respectively) and even higher in those belonging to G3 group ($p < 0.0001$ compared to control and G1, and $p = 0.0020$ compared to G2) (Fig. 2G). Increased NLR was also observed for non-T2DM (Fig. 2H) and non-obese patients (Fig. 2I) from G2 and G3. Importantly, no differences were observed in neutrophilia, lymphopenia, and in the NLR between T2DM and non-T2DM, and obese and non-obese patients from both G2 and G3 groups (Supplemental Fig. 3).

3.4. Erythrogram parameters are decreased in non-comorbid G3 patients

Because decreased hemoglobin levels can be a risk for severe respiratory failure of COVID-19 patients [28] and hemoglobin concentration is associated with the incidence of metabolic syndrome [29], we next evaluate the erythrogram of all studied individuals, and non-T2DM and

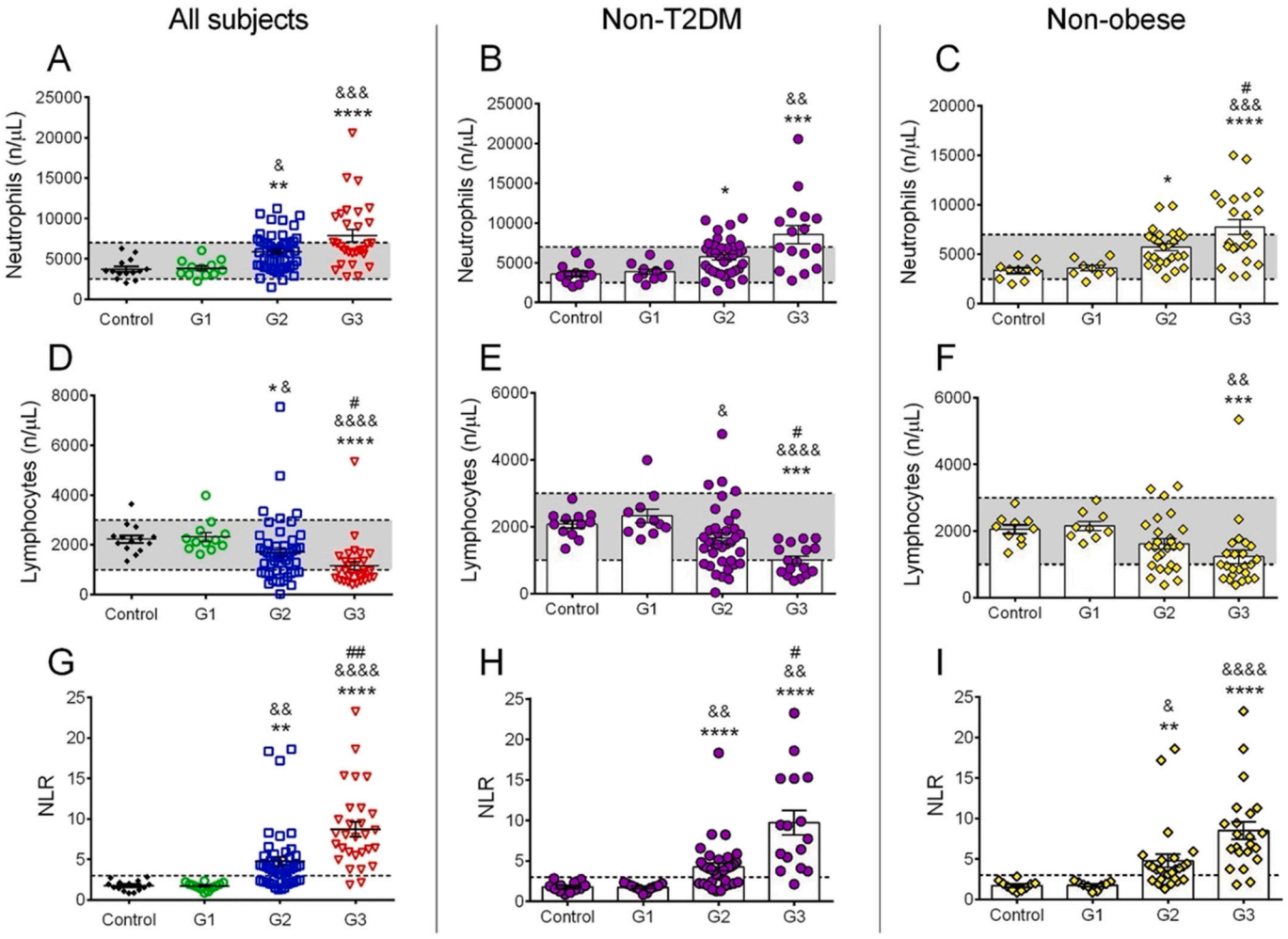

Fig. 2. Hemogram parameters according to the severity of the disease observed in COVID-19 patients with or without comorbidities. Serum from COVID-19 patients (G1: Group 1 – mild; G2: Group 2 – moderate, and G3: Group 3 – severe) or control individuals (Control) was obtained and used to quantify neutrophils (A–C) and lymphocytes (D–F), and to calculate the neutrophil to lymphocyte ratio (NLR) of all patients studied (A, D, G) or of non-T2DM (B, E, H), and non-obese (C, F, I) patients. Dashed line intervals indicate the normal range of neutrophil and lymphocyte numbers and the normal limit for NLR. Kruskal-Wallis test followed by Dunn's multiple comparison test for all graphs except C (One-Way ANOVA followed by Holm-Sidak's multiple comparison test). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, and ****$p < 0.0001$ compared to control group; &$p < 0.05$, &&$p < 0.01$, &&&$p < 0.001$, and &&&&$p < 0.0001$ compared to G1 group; #$p < 0.05$, ## $p < 0.01$ compared to G2 group.

non-obese patients. We observed a drop in hemoglobin (Fig. 3A), erythrocytes count (Fig. 3D) and hematocrit (Fig. 3G) in G3 patients when compared to control ($p = 0.0018$ in A, $p = 0.0002$ in B, $p = 0.0014$ in C), G1 ($p = 0.0216$ in A, $p = 0.0029$ in B, $p = 0.0317$ in C) and G2 ($p = 0.0061$ in A, $p < 0.0001$ in B, $p = 0.0034$ in C) subjects. When analyzing the erythrogram of patients without T2DM (Fig. 3B, E, H) or obesity (Fig. 3C, F, I), it was also verified a decrease in hemoglobin, erythrocyte count, and hematocrit of G3 patients in relation to control, G1 and G2 subjects with the following exception. In non-obese patients, hemoglobin (Fig. 3C) and hematocrit (Fig. 3I) from G3 patients were decreased when compared to control individuals only. No differences were observed between G3 patients with or without T2DM or obesity (Supplemental Fig. 4). Interestingly, when the G2 group was divided into patients who did not need oxygen support (G2A) and patients who needed it (G2B), we observed that erythrogram parameters were decreased in G2B compared to G2A patients (Supplemental Fig. 5A, D, G). This observed decrease was detected in T2DM patients (Supplemental Fig. 5B, E, H) and not in obese individuals (Supplemental Fig. 5C, F, I).

4. Discussion

Despite the specialized data produced during the COVID-19 pandemic and the effort of the health system professionals to understand the clinical manifestations of the disease, the precise pathogenesis of the infection and its outcomes are still under scrutiny. It was extensively observed that T2DM and obesity comorbidities worsen COVID-19 clinical manifestations, being considered as risk factors for the poor prognosis and outcomes of the disease [30,31]. On the other hand, both comorbidities may, in turn, cause and/or increase dyslipidemia, and increase the NLR in patients [21]. Dyslipidemia is also a risk factor for COVID-19 severe manifestation [31]. Although the link between obesity or T2DM and dyslipidemia is clearly understandable as aggravating factors for COVID-19 severity, as aforementioned, an expressive number of deaths occurred in non-comorbid patients [4]. Indeed, the results presented herein clearly suggest a positive association between lipid metabolic alterations and increased NLR with the COVID-19 severity. However, when excluding non-comorbid patients from the analysis, this association remains unaltered, suggesting that COVID-19 potentially leads to an atherogenic profile independently of comorbidities such as T2DM or obesity.

Dyslipidemia can be an inherited disease (genetic factor) or acquired

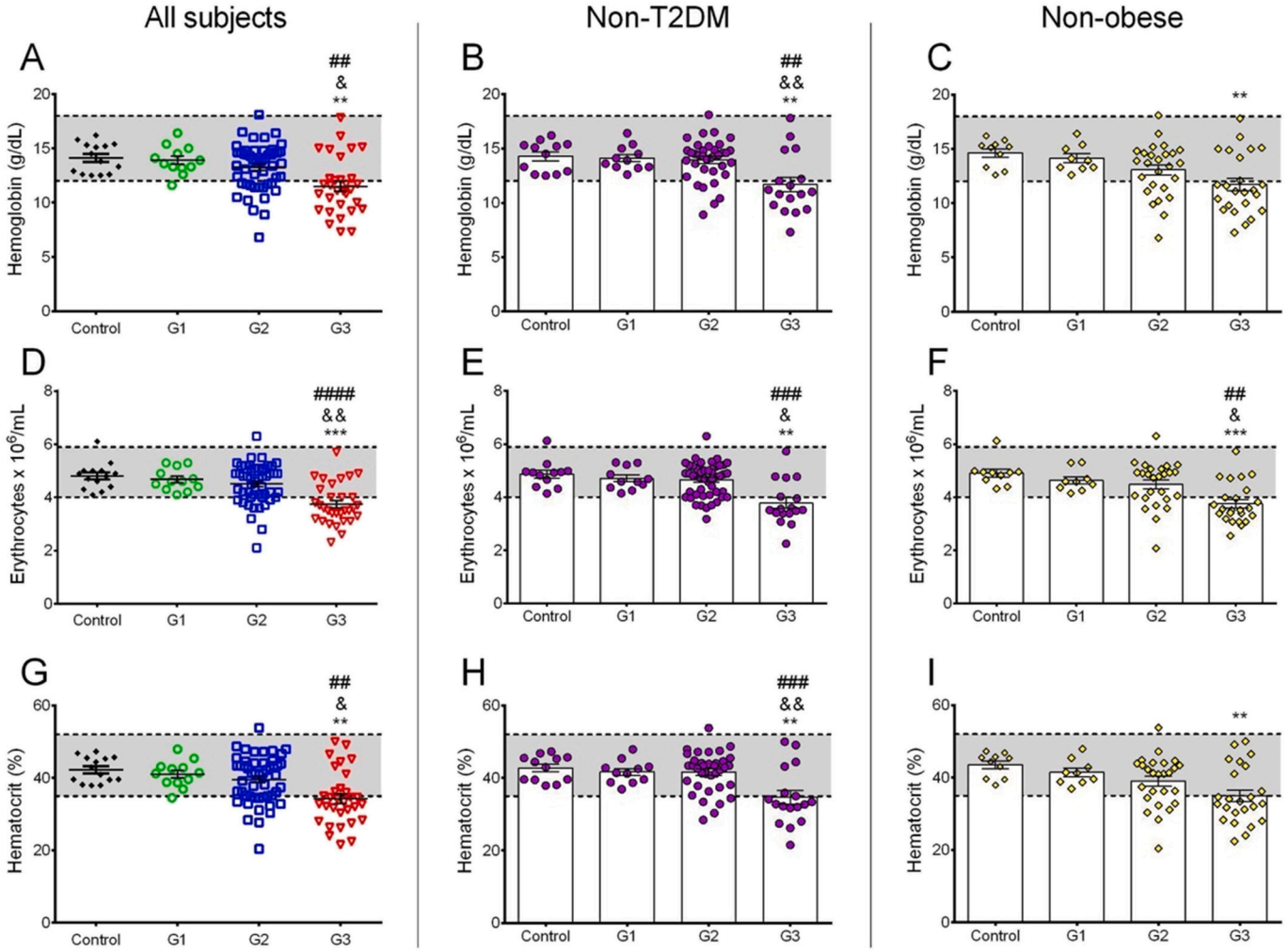

Fig. 3. Erythrogram profile of COVID-19 patients according to the severity of the disease and the presence of comorbidities. Serum from COVID-19 patients (G1: Group 1 – mild; G2: Group 2 – moderate; G3: Group 3 – severe) or control individuals (Control) was obtained and used to perform hemoglobin quantification (A–C), erythrocyte count (D–F), and hematocrit evaluation (G–I) of all patients studied (A, D, G) or of non-T2DM (B, E, H), and non-obese (C, F, I) patients. Dashed line intervals indicate the normal range of the erythrogram parameters evaluated. Kruskal-Wallis test followed by Dunn's multiple comparison test for A, D, F, G, H. One-Way ANOVA followed by Holm-Sidak's multiple comparison test for B, C, E, I. **$p < 0.01$, and ***$p < 0.001$ compared to control group; &$p < 0.05$, &&$p < 0.01$ compared to G1 group; ##$p < 0.01$, #### $p < 0.0001$ compared to G2 group.

through lifestyle and environmental factors exposure. Besides, it is known that the lipid profile may undergo modifications upon viral infections given the neutralizing role of lipoproteins on enveloped and nonenveloped viruses, conferring protection to the host [32]. However, this expected protective role of lipoproteins does not seem to work in COVID-19 patients, and may even worsen clinical manifestations and increase atherogenic risk. Our findings corroborate with other studies showing that the decrease of HDL cholesterol levels is correlated with the severity and mortality in cases of COVID-19 [33]. Additionally, it is known that lipid metabolic alterations can activate proinflammatory and coagulation factors, leading to the decrease of specialized pro-resolving mediators (SPMs) biosynthesis, endothelial dysfunction, platelet aggregation, and clot formation [34,35]. Thus, the proinflammatory profile of COVID-19 together with increased TG and VLDL, and decreased HDL, may favor the risk of atherothrombotic profile in moderate to severe patients. It is important to mention that increase in TG and VLDL serum levels, and decrease in TC and HDL levels is also observed in other infectious diseases, such as severe dengue [36], HIV [37], and sepsis [38,39], probably due to the cytokine storm induced by the infections.

The changes in the lipid profile associated with T2DM are attributed to increased free fatty acid flux secondary to insulin resistance; thus, the mortality from coronary heart disease in these patients is exponentially increased as a function of serum cholesterol levels [6]. In this sense, dyslipidemia associated with T2DM has a fundamental role in the development of atherosclerosis and cardiovascular diseases (CVDs) frequently observed in obese individuals. Likewise, dyslipidemia associated with obesity seems to be closely related to the insulin resistance in peripheral tissues leading to an enhanced hepatic flux of fatty acids originated from dietary sources. All these lipid abnormalities lead to a typical state of metabolic syndrome which is associated with a pro-inflammatory profile of the body [40]. Not by chance, excessive production of proinflammatory cytokines, known as the “cytokine storm”, is reported as one of the most aggravating and potentially life-threatening facts related to the COVID-19 [41]. Interestingly, analyzing the serum samples of non-T2DM and non-obese COVID-19 patients, we observed the same pattern of dyslipidemia in moderate to severe cases, indicating that the SARS-CoV-2 infection may potentially cause dyslipidemia within days to weeks post-infection. The precise mechanisms by which this phenomenon occurs need in-deep investigations.

Some hypotheses may explain the mechanisms involved in dyslipidemia induced by virus infection in general. Several cytokines, including TNF, IL-1, IL-6, and IFN-α, produced as a consequence of inflammation and infection, may increase TG levels by both increasing its production through a rapidly hepatic fatty acid synthesis, and/or decreasing its clearance [42,43]. A decrease in VLDL clearance was also demonstrated in experimental assays using lipopolysaccharide (LPS) to mimic gram-negative infections [43]. Infections, in turn, are also known to increase the oxidation of LDL. Oxidized LDL exerts several proatherogenic effects, being a possible mechanism for the high prevalence of coronary artery disease in patients with chronic inflammatory disorders and infections [44]. Under normal conditions, LDL is protected from oxidative stress by HDL-associated enzymes (particularly paraoxonase, an A-esterase) [45]; however, HDL levels are also decreased in COVID-19 patients, as shown by our results. Thus, the decrease of HDL and increase in VLDL levels may explain in part the cardiovascular manifestations of COVID-19.

In the past decade, the NLR became a marker of systemic inflammation linked to the risk of cardiovascular diseases [46] and correlated to the presence and severity of metabolic syndrome [21]. Knowing that COVID-19 is an inflammatory disease that potentially leads to cardiovascular impairment, the NLR of infected patients was analyzed. Independently of T2DM or obesity comorbidities, the NLR of moderate to severe patients was increased when compared to healthy individuals or mild COVID-19 patients reaching an almost 4-fold increase in severe cases. This data indicates that the SARS-CoV-2 infection triggers an inflammatory profile even in non-comorbid patients in a relatively short time post-infection.

Given the aforementioned results, we next hypothesized that inflammatory and lipid alterations experienced by COVID-19 severe patients would be affecting hematological parameters such as erythrocytes and hemoglobin, the most important players in oxygen and carbon dioxide transportation between the lungs and tissues which is strongly compromised in ICU patients. Erythrocytes also display an important role in immune mechanisms against SARS-CoV-2 infection capturing the virus through gangliosides and sialoglycoprotein glycophorin A (GPA) that act as receptors and deliver to macrophages for elimination [47]. Decreased hemoglobin concentration and erythrocyte number were observed in serum samples of G3 patients independently of T2DM or obesity preexistence. Knowing that hemoglobin affinity for oxygen is not altered during SARS-CoV-2 infection [48], this decrease in erythrogram parameters may explain in part the need for artificial ventilation experienced by COVID-19 ICU individuals [28]. Considering that, dyslipidemia has been associated with erythrocyte aggregation which may lead to a decreased life span of the cell [49], our data showing a reduction in erythrogram parameters in severe COVID-19 patients may be related to the reduction in HDL levels, also observed in non-comorbid patients.

Interestingly, moderate COVID-19 patients that needed oxygen support during hospitalization (G2B) presented a decrease in the erythrogram parameters compared to G2A patients. This decrease was especially observed in T2DM individuals, and not in obese ones. It is known that hemoglobin concentration is decreased in T2DM patients and associated with subclinical markers of atherosclerosis observed for T2DM [50]. Moreover, milder anemia can increase the risk of nephropathy in T2DM individuals [51]. Because acute kidney injury is frequent in hospitalized COVID-19 patients and associated with a high mortality rate [52], we can speculate that the decrease in hemoglobin observed in moderate to severe patients may contribute to a poor prognosis that can be worsened by the preexistence of comorbidities such as T2DM. It is important to point out that other erythrogram-related parameters such as mean cellular volume (MCV), erythrocyte distribution width (RDW), mean cellular hemoglobin (MCH), and mean cellular hemoglobin concentration (MCHC) were not altered amongst groups (Supplemental Fig. 6). Hence, the quantity of hemoglobin and erythrocytes are the key components in this scenario.

Although our data do not determine whether the alterations observed during infection were also present before the infection, they were strictly related to the severity of the cases. Particularly, it is worth mentioning that some of the current clinical drugs used for COVID-19 treatment, such as dexamethasone and remdesivir, may cause hyperglycemia [53] worsening the situation. In addition, the difference observed amongst groups regarding the interval of days for blood collection could be due to individual variability in the manifestation of the symptoms and the time of searching for medical assistance, as well as in obtaining the Free and Informed Consent form signed. These are limitations of the study. Nevertheless, the serum alterations observed in moderate and severe patients occurred within days after hospitalization, indicating that COVID-19 rapidly induces proatherogenic mechanisms even in non-comorbid patients.

Taken together, our data suggest that the COVID-19 serum alterations were not related to the presence of metabolic disorders in infected patients and, hence, would probably be caused by the infection. In this sense, controlling lipid alterations, especially HDL, at physiological levels at the early stages of the disease and monitoring the NLR together with hemoglobin concentration would be a low-cost strategy to ameliorate symptoms and reduce hospitalization and complications of COVID-19.

5. Conclusion

Our results endorse the relevance of lipid alterations, especially decreased HDL, increased NLR, and decreased hemoglobin

concentration as risk factors for severe outcomes in SARS-CoV-2 infection, independently of the presence of comorbidities such as T2DM and obesity. The identification and management of these alterations should be used as an early strategy to minimize COVID-19 worsening or even death.

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CRediT authorship contribution statement

GP, MBS, LFK, SAA- Conceptualization; RMGC, RFMV– recruitment of participants and clinical data collection; MCE, CL– data curation; GP, MBS, LFK– article writing; LFK, MBS– data analysis and statistics; all the authors - reading and correction of the manuscript.

Declaration of competing interest

Authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bcmd.2021.102604.

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