Containment measures established during the COVID-19 outbreak and its impact on lipid profile and neutrophil to lymphocyte ratio

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Abstract. – **OBJECTIVE:** Almost all countries announced social restrictions and distancing measures which could unintentionally lead to a decline in admissions to hospital for acute disorders other than signs of pneumonia. We aimed to evaluate lipid profile, neutrophil to lymphocyte ratio (NLR) and cardiovascular admissions to the coronary care unit (CCU) of a tertiary center in Turkey during the COVID-19 era and to compare these results with admissions in the same time interval of the previous year.

MATERIALS AND METHODS: We retrospectively analyzed CCU admissions due to new-onset atrial fibrillation, ST-elevation myocardial infarction, non-ST elevation acute coronary syndrome (NSTEACS) and acute heart failure during the COVID-19 outbreak and the same time interval of the past year. Laboratory measurements including lipid profile and NLR values were retrieved from the institutional digital database.

RESULTS: Compared to the same time interval of 2019 (March-April, 2019), the number of patients admitted to the CCU with acute cardiovascular disorders (atrial fibrillation, STEMI, NSTEACS and acute heart failure) were lower in the COVID-19 period. The levels of NLR, total cholesterol, and low-density lipoprotein (LDL) cholesterol were significantly higher and high-density lipoprotein (HDL) cholesterol was significantly lower in subjects admitted to the CCU during March-April 2020 compared to subjects admitted in March-April 2019.

CONCLUSIONS: Our findings show that subjects admitted to the CCU in the COVID-19 era have an unfavorable lipid profile and elevated NLR compared to those admitted in 2019. These patients appear to be at high risk for future cardiovascular events.

Introduction

Several cases of pneumonia of unknown etiology presenting predominantly with fever and cough emerged in Wuhan, Hubei Province, China towards the end of 2019[1,2]. Following the identification of a novel coronavirus in the throat swab sample of one patient by the Chinese Center for Disease Control and Prevention, the World Health Organization (WHO) named the novel coronavirus as 2019-nCoV[3]. The rapid spread of the disease within China and overseas was initially declared as a public health emergency of international concern (PHEIC) by the WHO. In February 2020, the virus was renamed as the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses[4]. Shortly after, the disease caused by SARS-CoV-2 was termed as coronavirus disease 2019 (COVID-19) by the WHO.

As of June 25, 2020, COVID-19 was confirmed in around 10 million individuals worldwide and had caused over 500,000 fatalities[5]. Although COVID-19 primarily affects the lungs, cardiovascular involvement has also been reported[6]. Direct myocardial cell injury, myocardial oxygen supply/demand mismatch, acute plaque rupture leading to acute coronary syndrome (due to excessive

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systemic inflammation and catecholamine surge), increased thrombosis, and the potential side effects of medications that were being used for the treatment of the COVID-19 are considered to play some role in cardiac manifestations[7]. On the other hand, COVID-19 and chronic cardiovascular disease often co-exist, demonstrating the vulnerability of this population[8].

This relationship between COVID-19 and cardiovascular diseases may give rise to the expectation that cardiovascular admissions would increase as the infection spreads, particularly when compared to previous years. However, almost all countries declared a state of alarm and announced social restrictions and distancing measures which may have unintentionally lead to a decline in hospital admissions for acute disorders other than those involving the respiratory system. In Turkey, individuals aged <20 years and >65 years were restricted to their homes as part of the initial social distancing measures since the older population is a vulnerable group for COVID-19 and the young population was considered as an important vector of disease spread. With regard to the health system, elective interventional and surgical procedures were postponed due to the heavy burden expected from COVID-19. Due to the adoption of these measures and fear of being infected by SARS-CoV-2 in hospitals, clinics and emergency departments, patients might have refrained from seeking medical help even when they had signs of acute cardiovascular disorders.

Therefore, we evaluated cardiovascular admissions to the coronary care unit (CCU) of a tertiary center in Turkey with the primary aim of comparing the frequency of admissions before and after COVID-19.

Materials and Methods

This study was conducted following the approval of the Local Ethics Committee and after necessary permissions were obtained according to the Ministry of Health regulations. On March 10, 2020, after the first case of COVID-19 was confirmed in Turkey, the Ministry of Health began publishing containment measures for the general public. From this point on, individuals aged <20 years and >65 years were forced to stay home until further notice.

Taking this date as a threshold, we evaluated CCU admissions for acute cardiovascular disorders (new-onset atrial fibrillation, ST-elevation myocardial infarction, non-ST elevation acute coronary syndrome) from March 10, 2020 to May 2, 2020. The number of CCU admissions, first diagnoses, coronary interventions performed during index hospitalization, and laboratory measurements were retrieved from the institutional digital database. Subjects who were not considered to have an acute cardiovascular disorder were excluded. For the comparison group, CCU admissions due to an acute cardiovascular disorder within the same time interval of the previous year (March 10, 2019-May 2, 2019) were retrieved from the institutional digital database. The difference in CCU admissions due to acute cardiovascular disorders between the same time intervals of 2019 and 2020 was the primary outcome measure of this study.

Statistical Analysis

All analyses were performed on SPSS Version 21 (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was used to determine whether or not variables were normally distributed. Data were given as mean ± standard deviation or median (minimum maximum) for continuous variables according to normality of distribution, and as frequency (percentage) for categorical variables. Continuous variables were compared using the independent samples *t*-test, and categorical variables were compared using the Pearson chi-square test. *p*-values of less than 0.05 were considered statistically significant.

Results

Compared to the same time interval in 2019 (March-April, 2019), the number of patients admitted to the CCU with acute cardiovascular disorders (atrial fibrillation, STEMI, NSTEACS and acute heart failure) was lower in the COVID-19 era. The age and gender distribution of subjects, and the frequencies of atrial fibrillation, STEMI, NSTEACS and acute heart failure were similar in the two time-periods (Table I). Total cholesterol and low-density lipoprotein (LDL) cholesterol were significantly higher, while high-density lipoprotein (HDL) cholesterol was significantly lower in subjects admitted to the CCU during March-April, 2020 compared to subjects admitted in 2019 (Figures

Table I. Summary of patients characteristics and biochemical measurements.

	CCU admissions March-April 2019 n = 243	CCU Admissions March April 2020 n = 164	*p*-value
Age, years	63.2 ± 8.1	61.5 ± 9.8	0.144
Gender, male	168 (69%)	114 (69%)	0.936
Final diagnosis			
Atrial Fibrillation, n	17 (7.0%)	6 (3.7%)	0.274
STEMI, n	60 (24.7%)	49 (29.9%)	
NSTEACS, n	141 (58.0%)	97 (59.1%)	
Acute HF, n	25 (10.3%)	12 (7.3%)	
Troponin, ng/mL	5.7 ± 1.3	7.4 ± 1.7	0.289
Creatinine, mg/dL	0.99 ± 0.13	1.06 ± 0.18	0.176
HDL cholesterol, mg/dL	45.3 ± 8.9	39.5 ± 7.4	0.028
LDL cholesterol, mg/dL	98.5 ± 14.6	114.3 ± 27.2	< 0.001
Triglyceride, mg/dL	141.3 ± 24.7	140.2 ± 18.9	0.914
Total cholesterol, mg/dL	165.5 ± 22.6	181.4 ± 25.3	0.001
Leukocyte count, n	9.4 ± 1.1	9.8 ± 1.5	0.246
Hemoglobin, g/dL	14.9 ± 2.3	14.5 ± 2.7	0.744
Neutrophil count, $10^3/mm^3$	7.2 ± 0.9	7.4 ± 1.1	0.821
Lymphocyte count, $10^3/mm^3$	2.6 ± 0.5	1.8 ± 0.3	0.012
NLR	4.6 ± 1.2	5.7 ± 1.6	0.043
CRP	21.72 ± 40.59	22,64 ± 39.30	0.607

Data are presented as the mean standard deviation for continuous variables and as frequency (percentage) for categorical variables. CCU=Coronary care unit, HDL=High density lipoprotein, LDL=Low-density lipoprotein, NLR=Neutrophil to lymphocyte ratio, CRP=C-reactive protein.

1 and 2). Neutrophil to lymphocyte ratio (NLR) was also found to be significantly higher in subjects admitted to the CCU in the March-April 2020 time period when compared to 2019 (Figure 3).

Discussion

These findings show that the number of admissions to the CCU of our institute with acute cardiovascular disorders, such as atrial fibrillation,
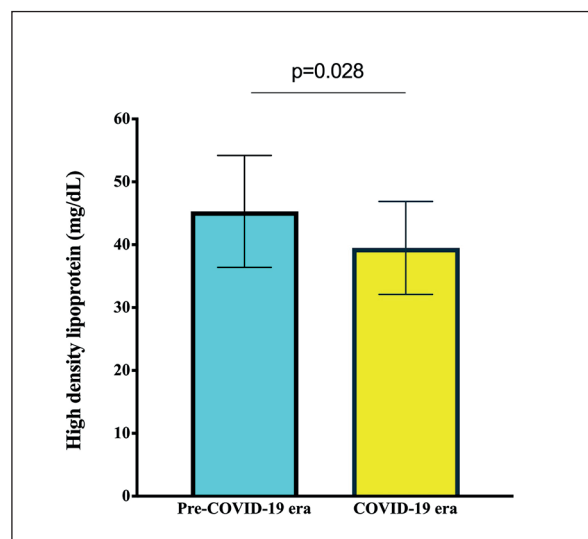

Figure 1. The distribution of High-density lipoprotein (HDL) cholesterol levels according to pre-COVID-19 and COVID-19 era.
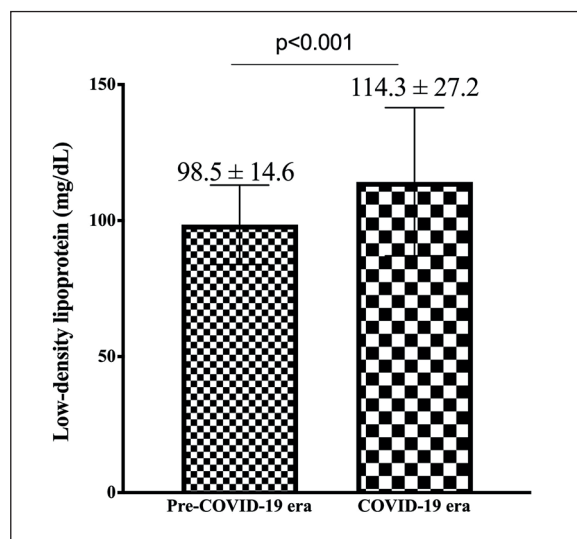

Figure 2. The distribution of Low-density lipoprotein (LDL) cholesterol levels according to pre-COVID-19 and COVID-19 era.
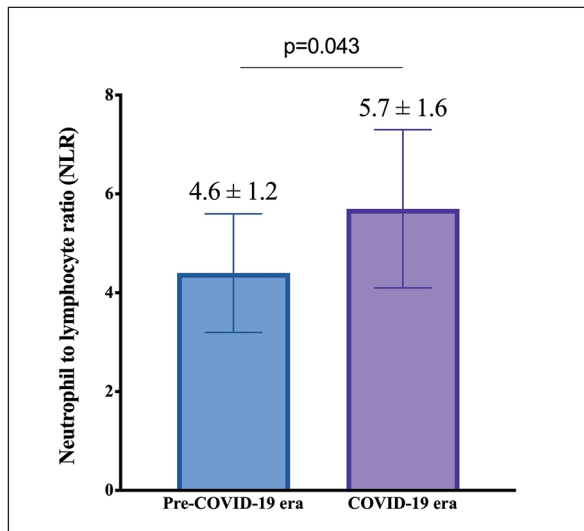
Figure 3. The distribution of neutrophil to lymphocyte ratio (NLR) according to pre-COVID-19 and COVID-19 era.

STEMI, NSTEACS and acute heart failure, were lower in the COVID-19 era compared to the same time interval in 2019. Moreover, HDL cholesterol was significantly lower and LDL cholesterol, total cholesterol and NLR were significantly higher in subjects admitted to the CCU in the COVID-19 era when compared to those admitted in 2019.

Patients with a history of cardiovascular disease are at high risk for worse prognosis when diagnosed with COVID-19[9-11]. Although the causes of increased complication rates in this population are not completely clear, the clustering impact of hypertension, diabetes, smoking, male gender, and obesity have been identified as factors associated with poor outcomes in patients diagnosed with COVID-19 who had pre-existing cardiovascular diseases[12,13]. Additionally, COVID-19 has also been suggested to facilitate the development of various acute cardiovascular conditions, such as pericarditis, myocarditis, myocardial infarction, heart failure, arrhythmias or thromboembolic events[14]. Apart from the direct or indirect effects of the disease itself, it is possible that government-imposed restrictions led to a lack of regular physical activity, unhealthy eating habits and sudden increase in body weight all of which could ultimately result in higher risk for the development of acute cardiovascular disorders[15]. One could, therefore, easily expect that admissions due to cardiovascular diseases would increase in the COVID-19 era.

In contrast to this general expectation, a number of studies have shown that emergency department referrals due to acute cardiovascular disorders have significantly declined following the establishment of safety measures aiming to prevent the spread of the COVID-19. A recent report[16] from France revealed that the number of subjects admitted to the nine participating intensive CCUs declined from 4.8 ± 1.6 patients per day to 2.6 ± 1.5 per day after the establishment of containment measures. A multicenter observational study from Italy reported that there was a 48.4% reduction in the number of admissions for acute myocardial infarction compared to the corresponding week in 2019[17]. In Austria, the comparison of the number of patients admitted with acute coronary syndrome from the 10th to the 13th calendar weeks of 2019 and 2020 demonstrated a relative reduction of 39.4% in the post-pandemic period[18]. Data from a study involving nine high-volume cardiac catheterization laboratories in the United States reported an average of 38% reduction in STEMI applications after COVID-19 compared to the pre-COVID-19 era[19].

The strict self-isolation and quarantining measures recommended by national health authorities appear to have unintentional results, such as hesitating to seek medical help even for potentially serious medical conditions[20]. Consistent with the published data, our findings indicate that CCU admissions due to acute cardiovascular disorders declined dramatically following the introduction of state-mandated self-isolation measures. It appears that the declaration of containment measures and the fear of exposure have created a state in which patients are reluctant to apply to hospitals. There are also several other explanations for these results. First, it is possible that patients diagnosed recently (who did not develop disease-related complications) were seeing the risk of exposure to COVID-19 as a worse alternative. Likewise, patients followed for a longer time with the cardiac disease could be accustomed to their disease state; thus, they could not apply to a hospital with relatively less-severe complaints. Considering the high possibility that these measures will more or less remain in place for the near future, it is important that policy makers make efforts to increase public knowledge about the risks of refraining from accessing medical care in potentially serious situations.

Our findings also show that subjects admitted to the CCU in the COVID-19 era have significantly worse lipid profile and higher NLR compared

to subjects admitted in the same period of 2019. These poor laboratory results may be associated with limited access to medications, reduced compliance with therapy, poor eating habits and reduced physical activity. Therefore, although these measures decrease the spread of COVID-19, they may have inadvertently increased risk factors for cardiac disease. Given the strong relationship between unfavorable lipid profile and cardiovascular mortality, it is apparent that prolonged self-isolation measures may result in an increase in the prevalence of insulin resistance, diabetes, hyperlipidemia, hypertension, peripheral and coronary vascular disease, and stroke[21-23]. In addition to identifying unfavorable lipid results, our study showed elevated NLR values in the post-COVID-19 population admitted to the CCU. An elevated NLR, which is frequently encountered in subjects with a sedentary lifestyle and reduced exercise capacity, is an indicator of inflammatory activation[24-27]. NLR has been shown to predict the extent and severity of coronary artery disease and adverse events in subjects with acute coronary syndromes[28-30]. Accordingly, increased NLR in subjects admitted to the CCU in the COVID-19 era may be predictive for future cardiovascular events.

An integrated healthcare system should not only focus on the COVID-19 outbreak but must also consider the impact of containment measures on the general well-being of individuals who are at high risk for cardiovascular diseases. Every effort, including structural changes in public recreation areas, should be carried out to reduce possible unfavorable outcomes related to the adverse effects of containment measures.

Conclusions

Our findings show that a dramatic decline has occurred in the frequency of CCU admissions during the COVID-19 outbreak. The state of alarm declared by many countries and public service announcements may have increased hesitancy when seeking medical care for life-threatening cardiovascular disorders. Our findings also show that subjects admitted to the CCU in the COVID-19 era have an unfavorable lipid profile and elevated NLR compared to those admitted in 2019, which may be associated with difficulties in acquiring medication, limited physical activity and unhealthy nutritional habits. These patients appear to be at high risk for future cardiovascular

events. We believe that health authorities and policymakers should focus on the possible negative cardiovascular consequences of the containment measures when assessing their success in the prevention of the spread of COVID-19.

Ethical Approval
All procedures performed in this study were in accordance with the Ethical Standards of the Institutional and/or National Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent
Informed consent was obtained from all individual participants included in the study.

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