Neck Circumference Predicts Mortality in COVID-19 patients

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A large neck is associated with a premorbid increased proinflammatory and prothrombotic status, which makes the patient more prone to progress toward an unfavorable outcome. Neck circumference is an independent predictor for mortality in our hospitalized COVID-19 patients with respiratory failure and should complement the baseline evaluation of such patients.

Keywords: neck ; neck circumference ; COVID-19 ; mortality ; BMI ; metabolic syndrome

1. Introduction

The SARS-CoV-2 pandemic, beginning in Wuhan (China) in December 2019, is still creating huge difficulties for the healthcare services of several countries worldwide. The clinical manifestations of the coronavirus disease 2019 (COVID-19) are heterogeneous, ranging from mild diseases to extensive pulmonary disease manifesting as acute respiratory distress syndrome which may lead to death. Despite the availability of new therapeutic options, COVID-19 mortality remains high [1], especially in hospitalized patients with pneumonia who require oxygen therapy support. Severe and fatal COVID-19 episodes are more prevalent among elderly individuals with cardiometabolic and respiratory comorbidities such as hypertension, chronic lung disease and diabetes [2][3]. Notably, most of these concomitant diseases constitute the definition of metabolic syndrome, a common metabolic disorder in the general population. In terms of COVID-19 treatment, at the present time, the most effective drug in terms of mortality reduction is dexamethasone, able to reduce the inflammatory immune-mediated pathogenic process that characterizes the second phase of the disease [4]. Heparin use at therapeutic doses did not show encouraging results, possibly for a timing issue or for the intrinsic characteristics of COVID-19 pulmonary thrombi (phlogistic platelet-rich “white thrombi”) [5]. It has been demonstrated that hormonal and metabolic features have a significant impact on the clinical progression of COVID-19 patients. In fact, male subjects with COVID-19 have a higher mortality risk than female subjects, with 60–70% of COVID-19 associated deaths occurring in men [6]. In addition, from a metabolic point of view, it is well known that the body mass index (BMI) correlates with a worse prognosis among COVID-19 patients [7], however, BMI measurement as a prognostic tool has some limitations since it disregards the fat distribution. In fact, more than the mere BMI, is the fat distribution to reflect a dysmetabolism oriented toward metabolic syndrome. Current findings confirm that upper body fat is a good predictor of metabolic syndrome [8] with several studies demonstrating upper-body obesity to have a stronger association with cardiometabolic conditions compared to lower-body obesity. Patients with a central obesity distribution have a higher risk of hypertension, type 2 diabetes, obstructive sleep apnea syndrome, and non-alcoholic fatty liver diseases. Metabolic syndrome is a pathologic condition characterized by abdominal obesity, insulin resistance, hypertension, and hyperlipidemia. The precise global prevalence of metabolic syndrome is difficult to measure but it is estimated to be about one-quarter of the world population [9]. It is well known that metabolic syndrome is associated with an increase in pro-inflammatory cytokines (IL-6, TNF-α), markers of pro-oxidant status (OxLDL, uric acid), and prothrombotic factors (PAI-1) [10]. Moreover, C-reactive protein (CRP) strongly correlates with upper body fat [8] and neck circumference is associated with upper body fat (central body obesity) [11]. In addition, neck circumference has been shown to be strongly related to insulin resistance, early-stage atherosclerosis, diabetes, coronary heart diseases, and cardiometabolic syndrome even after adjustment for visceral adipose tissue and BMI [12]. In a previous study on 132 COVID-19 patients, we demonstrated that neck circumference measured on admission is independently and significantly associated with the progression to mechanical ventilation (adjusted OR 1.26-per 1 cm increase; 95% CI: 1.120–1.417; $p < 0.001$) [13]. At that time our sample was too small to investigate the relationship between neck circumference and mortality. In the present study, with a larger sample size, we aimed to assess if neck circumference measured on hospital admission correlates with the occurrence of short- and mid-term mortality among COVID-19 hospitalized patients, thus investigating its potential as a cheap and easy-to-use prognostic predictor.

2. Current Insights

Indeed, the pathogenesis of this new viral disease seems to be more related to a dysregulated immune and inflammatory response than to direct viral tissue damage. The association between dysmetabolism (e.g., metabolic syndrome) and baseline inflammation and prothrombotic state is supported by robust data. In terms of “prothrombotic state”, it has also been demonstrated that venous and pulmonary thromboembolism are common complications of COVID-19 (approximately 30% of hospitalized patients) with a significant impact on clinical outcome. Many studies demonstrated that the specific patterns of “excess fat distribution” conferred different metabolic risks, pointing out the pro-inflammatory role of visceral adipose tissue and upper body adiposity. When facing infectious disorders, the fat excess can impair the immune system response through a chronic basal inflammatory status and it has been hypothesized that specific fat depots could increase the vascular damage [14][15]. Males are more susceptible to upper-body fat accumulation, due to sex hormone differences and males are more susceptible also to a complicated/fatal COVID-19 clinical progression. Neck circumference is an emerging anthropometric parameter that has been proposed to reflect human metabolic health [16]. Neck circumference is considered a proxy for central body obesity, which is considered the “most harmful” obesity. In our cohort, in the present study, patients with a “large neck” phenotype had a statistically significant higher prevalence of arterial hypertension, diabetes, obesity, and high CRP levels. In the present investigation, only a moderate—although statistically significant—correlation between BMI and NC was found, meaning that BMI cannot substitute NC, and vice-versa. However, compared to BMI, NC may be a more accurate and easy-to-measure marker of adiposity and metabolic risk in daily clinical practice (e.g., weighing a patient under mechanical ventilation may not be simply feasible, measuring her/his height while lying in a bed may lead to more imprecise data than gauging an NC). Moreover, we believe that neck circumference could outperform the prognostic predictive value of BMI among COVID-19 patients, being more associated with a specific fat distribution pattern, thus reflecting a “bad” obesity distribution pattern. Interestingly, a large neck circumference has been significantly associated with the prevalence of obstructive sleep apnea syndrome [17]. According to the literature data, obstructive sleep apnea syndrome occurs in 2–4% of adults, increasing by 2.5 times the risk of sudden death. When looking at SARS-CoV-2-infected patients, a recent study showed that there was an increased risk of mortality in COVID-19 patients with obstructive sleep apnea syndrome (OR = 2.59; 95% CI 1.218–5.507) independently from BMI, male gender, age, diabetes, cardiovascular diseases, and obstructive lung disease [17]. It is possible that part of the risk is attributable to the fact that, since gasping is a common phenomenon in patients with obstructive sleep apnea syndrome, this can predispose to aspiration of viral particles [18]. Furthermore, also other mechanical problems in obstructive sleep apnea syndrome contribute to less effective ventilation treatment, including a higher risk of difficult intubation and non-invasive ventilation may be less effective due to the intermittent airway obstruction episodes [19]. In addition, higher levels of inflammatory markers have been reported in obstructive sleep apnea syndrome patients compared to patients without obstructive sleep apnea syndrome [20]. This could increase the risk for overproduction of early response proinflammatory cytokines which could increase the chances of developing cytokine storm syndrome [21]. In our series, COVID-19-hospitalized patients with respiratory failure and a large neck phenotype had a more than double risk of death (both at 30 and 60 days). Given the doubts on the best predictive measure, including both NC and BMI in the multivariable model despite a potential collinearity problem, showed that NC seemed to outperform BMI in predicting mortality. Although we were confident to have reduced this risk by inserting BMI and NC as categorical variables, this aspect should be considered when interpreting the results of the first regression analysis. However, NC confirmed its predictive power in further models run after excluding BMI.

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