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EDITORIAL

COVID-19 SPIRALING OF FRAILTY IN OLDER ITALIAN PATIENTS

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The world aging population is continuously rising and Italy is the second country following Japan with the largest concentration of persons living over the age of 65 years (1). At the moment, 22.4% of the Italian population is over the age of 65 years. Even though reaching advanced age in any country should be considered a significant and outstanding accomplishment, such triumph does not seem to come without sacrifice. Advanced aging is also accompanied by the increase in the risk of numerous comorbidities, such as arterial hypertension, heart disease, dementia, osteoporosis, cancer, Type 2 Diabetes, as well as other disease states that require continuous medical treatment. Most of these treatments require individual geriatric care modeling in order to maintain a "healthy" equilibrium necessary to avoid the irreversible spiral of the Frailty Syndrome. Frailty has been defined as a "syndrome characterized by a clinical state in which there is an increase in an individual's vulnerability for developing an increased dependency and/or mortality when exposed to a stressor" (2). Frailty should be considered a constantly evolving syndrome and only reversible if appropriate intervention is quickly recognized and applied. Indeed, there is substantial literature underlining the importance of geriatric medicine toward frailty prevention and clinical criteria to rapidly identify those with frailty or pre-frailty (3-5). If any negative health conditions break the equilibrium, the irreversible downward spiraling of frailty will begin. Over the last few months, there has been a worldwide rise infection of Coronavirus disease (COVID-19). As of March 27th, the country of Italy has over 79,900 persons infected with COVID-19 and 7590 deaths associated with COVID-19. Therefore, due to the rapid spread of the coronavirus in Italy, there seems to be a deadly trend toward mortality with COVID-19 in older patients with specific comorbidities, thus identifying a new "COVID Spiraling Frailty Syndrome". This brief commentary will provide recent findings related to age-related comorbidities commonly found in advanced age and their percentages in older Italians that have recently died with a COVID-19. We will also consider potential aspects of different drugs for such comorbidities and COVID-19. This commentary specifically focuses on the Italian population of older patients in the last month of disease spread.

The COVID spread in Italy

At the moment, the epidemic in Italy of COVID-19 continues to spread throughout the entire country. According to data from the Italian Istituto Superiore di Sanità (ISS) infection has continuously grown higher since the latter half of the month of February 2020 (6). As of March 27th, there are still growing cases of infection with a higher trend in men (58%) and 35.8% of those with infection are ≥ 70 years of age.

Of those that have died with COVID-19 (n=7589), 83.7% (n=6351) were ≥ 70 years, while 16.2% (n=1238) were < 69 years (6). Therefore, older age even in Italy would seem to hold an important risk for infection and mortality (7).

It is widely known that Aging is associated with an increased risk for diverse comorbidities. Considering that infection from COVID-19 is strongly associated with severe acute respiratory syndrome (SARS), it would seem obvious that patients with depressed immune response, such as in those patients with Chronic Obstructive Pulmonary Disease (COPD) or Chronic Renal Insufficiency would be at a significantly higher risk for SARS. However, available data from the ISS show that the most common comorbidities observed in all Italians dying with COVID-19 are arterial hypertension (74.7%) and Type 2 Diabetes (30.5%) (6). Interestingly, the same comorbidities have also been found to hold high percentages in Chinese retrospective data from COVID. For example, Yang X et al. (8) found that in 52 non-survivors with COVID-19, 22% had Type 2 Diabetes, while another study found that hypertension was the most common comorbidity reaching 30% in a sample of 191 patients (9). In recently published Chinese report, regarding an in-hospital sample of older persons (n=4,348) with a mean age of 74 years, found that hypertension was the most common comorbidity (63.1% prevalence) and increased to 72.5% in over 80 year olds from Wuhan (10). Indeed, both hypertension and Type 2 Diabetes were associated with a higher odds ratio of in-hospital death with COVID-19 (9). Unfortunately, data regarding regular drug regimens for these comorbidities prior to hospitalization in those dying with COVID in these studies was not assessed. In 2017, a Chinese study underlined that in over a million patients, the most commonly used anti-hypertensive agent was calcium-channel blockers (11).

In addition, patients with COPD had a 5- to 6-fold increase

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in the ratio of angiotensin receptor-1 (AT-1) to angiotensin receptor-2 (AT-2) in pulmonary regions with marked fibrosis (12). AT-2s have been shown to hold anti-fibrotic properties, while AT-1s seem to hold a role in COPD-lung induced fibrosis (12). Angiotensin converting enzymes 2 (ACE-2) are expressed on myocytes, renal endothelial and epithelial lung cells (13) and have shown to act as receptors for SARS-CoV-2 (14). Thus, one may hypothesize a direct involvement of the virus on cardiac muscle tissue, endothelial and epithelial cells. In addition, it has been suggested that angiotensin 2 type 1 receptor blockers (ARBs) may increase ACE-2 expression and target host response to infection (15). However, ARBs have been shown to improve on endothelial dysfunction by increasing levels of Angiotensin-(1-7), a vasodilator especially present in increased ACE-2 expression (16). At the moment, future studies are needed to identify the pathways related to a potential role of ACE-2 expression on facilitating COVID-19 infection in those undergoing drug treatments with ACE inhibitors and ARBs for hypertension.

At the moment, older patients with diabetes seem to have a significantly higher risk of mortality with COVID-19. Over the years, there has been substantial data underling an important role of the renin-angiotensin system (RAS) on glycemic control (17). In particular, ACE-2 seems to play a role on blocking Angiotensin II- mediated hyperglycemia. ARBs and ACE inhibitors improve glycemia by blocking RAS over activity. It has been recently highlighted that ACE-2 is increased in patients with diabetes undergoing treatment with ACE inhibitors and ARBs (13). The underlying question remains if the increased expression of ACE-2 can protect or increase the risk of the development and mortality associated with COVID-19!

Testing which specific anti-diabetic oral agents are correlated with COVID-19 and mortality in older patients will add novel insight.

The potential "COVID Spiraling Frailty Syndrome"

The use of the clinical phenotypes for identifying the Frailty Syndrome in the aging population has gained substantial and important clinical guidance over the past years. However, geriatric medicine is now being faced with a new worldwide enemy, COVID-19, that together with older age, hypertension and Type 2 Diabetes may clinically define the "COVID Spiraling Frailty Syndrome". Therefore, there is an urgent need to analyze available data in Italy as well as, worldwide to test for potential correlations before and during in-hospital drug treatments (especially those for hypertension and diabetes) in order to protect against mortality in older COVID patients. Future investigations will also need to investigate the level of clinical stability according to drugs before and during hospitalization.

Centenarians and COVID-19

Interestingly, a 102 year-old Italian women with COVID, who has experienced in her lifetime two world wars, was discharged from the hospital on March 27th in Northern Italy (18). There have also been two reported cases of Chinese centenarians (one female and one male) that have recovered from COVID in Wuhan (19). Centenarians continue to hold secrets, which underline important visions for future geriatric medicine worldwide and the hope for thumping from COVID in very old patients.

Future perspectives

At the moment, all countries are in need of fast and accurate tests for COVID-19. The increasing need for elders to move into assisted living and nursing homes is constantly rising. The use of a quick and reliable test for COVID-19 would quickly allow these elders to be rapidly placed in necessary living environments. Therefore, there is an urgent need for rapid COVID testing in order to allow elders to safely travel (by car, air, train etc.) to reach such appropriate living settings. However, this is only one of the many interventions geriatric patients wait for in order to survive and to maintain a good health. Geriatricians have to cope with a great variety of important clinical and research needs either directly or in cooperation with other specialists (Box 1).

Box 1

Future aspects of geriatric medicine in older persons with COVID

- cost/benefit analysis of selected drugs likely to affect the course of Covid19 infection;
- detection of early warning in patients with chronic diseases;
- systems for remote monitoring of isolated patients;
- teleconsulting for chronic conditions;
- standardized safety measures in nursing homes;
- psychological support for selected patients;
- assessment and definition of variant presentations in multi-morbid patients;
- defining age-specific ventilatory assistance;
- profiling risks with comprehensive geriatric assessment;
- test recognized markers of frailty are related to COVID outcomes;
- assessment of residual effects (i.e sensorial, cognitive, emotional) in survived patents;
- prevention of major changes in life style and worsening living facilities of survived patients.

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