Reviews/Focus on

Assessment and treatment of older individuals with COVID-19 multi-system disease: clinical and ethical implications

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Summary. Covid-19 infection is a multisystem disease more frequent in older individuals, especially in those with multiple chronic diseases. This multimorbid and frail population requires attention and a personalized comprehensive assessment in order to avoid the occurrence of adverse outcomes. As other diseases, the COVID-19 presentation in older patients is often atypical with less severe and unspecific symptoms. These subjects both at home and during hospitalization suffer isolation and the lack of support of caregivers. The geriatric care in COVID-19 wards is often missing. The application of additional instruments would be necessary to facilitate and personalize the clinical approach, not only based on diseases but also on functional status. This narrative review starts from diagnostic evaluation, continues with adapted pharmacologic treatment and ends with the recovery phase targeting the nutrition and physical exercise. We developed a check-list of respiratory, gastrointestinal and other less-specific symptoms, summarized in a table and easily to be filled-up by patients, nurses and general practitioners. As second step, we reported the clinical phases of this disease. Far to be considered just viral infective and respiratory, this disease is also an inflammatory and thrombotic condition with frequent bacterial over-infection. We finally considered timing and selection of treatment, which depend on the disease phase, co-administration of other drugs and require the monitoring of renal, liver and cardiac function. This underlines the role of age not just as a limitation, but also an opportunity to increase the quality and the appropriateness of multidisciplinary and multidimensional intervention in this population. (www.actabiomedica.it)

Key words: Covid19, Elderly, Frailty, Polypharmacy

Epidemiology and Specificity of COVID 19 in older Population

COVID-19 infection is a multisystem disease especially severe in older individuals with multiple and chronic diseases.

Morbidity and mortality due to COVID-19 have had different impacts worldwide, with huge differences between Eastern and European and Western countries. Case counts and deaths are soaring in Italy, Spain, France and USA while they have dropped sharply in China and South Korea (1).

These countries differ in terms of percentages of population over 65, the most afflicted by infection, with Italy reaching 23%. Italy for instance has higher life expectancy than the majority of countries affected by COVID-19 infection (83.4 overall vs 76.7 in China) (2).

These demographic differences could also explain the different outcomes between countries. Italy has one of the highest COVID-19 mortality (26,644 deaths) and case-fatality rate (7.2%), much higher than China (2.3%). Interestingly, the case-fatality rate in Italy and China are very similar for age-groups 0 to 69 years, but rates are higher in Italy especially among those aged 80 years or older (52% of deaths and 20% of case fatality rate). This difference can be at least partially explained by the higher number of people aged 80 years or older (n=11563), age group having a very high fatality rate (22.7%) and not reported in China (2).

Gender issue has been raised by scientists and epidemiologists with men experiencing higher prevalence (64.2 % in the last Italian Report) and severity (they die more and at earlier age) of COVID-19 infection than women. Many hypotheses have been formulated to explain this difference between two sexes. COVID-19 virus can be localized in the testes, which are potential target of SARS-CoV-2 infection, and one of the reasons for the rapidly spreading disease. Moreover, testosterone, the male hormone, has been shown to upregulate the expression of transmembrane protease, serine 2 (TMRPSS2) which is an enzyme involved in the penetration of virus in the lung cells.

Age is accompanied by changes in immune competence and a higher prevalence of inflammation, so-called "inflammaging" (3). The chronic increase in inflammatory cytokines, augmented by COVID-19 infection, may explain the higher tendency for "the cascade leading to pulmonary fibrosis and insufficiency and activation of clotting" and poorer clinical prognosis, especially in multimorbid older persons (4).

Multimorbidity defined by the concomitant presence of two or more chronic diseases, is highly prevalent in older persons, affecting more than 60% of people aged 65+ (5). Data collected in 21.551 SARS-CoV-2 Italian patients who died from COVID-19 show that the mean number of diseases is 3.2 (median SD 3 ±1.9). Seventy patients (3.7 % of sample) had no diseases, 273 (14.4%) 1 disease, 400 (21.2%) 2 diseases, and 1147 (68.7%) 3 or more (2). Cardio-renal-respiratory (heart failure, atrial fibrillation, chronic renal failure, COPD), metabolic diseases (obesity and type 2 diabetes), active cancer during the last 5 years and dementia seem to be the clusters more associated with adverse clinical outcomes.

As a consequence of multimorbidity, polypharmacy defined as the number of drugs reported at hospital admission and the potential drug-drug interactions require a careful evaluation in older COVID-19 patients. The combination of antiviral and anti-inflammatory drugs (never tested before in these individuals) and the concomitant treatment for other chronic diseases, especially in subjects with smoking exposition or sarcopenic obesity, increase the risk of adverse drug effects. Diarrhea, dehydration, acute kidney insufficiency and liver failure can frequently occur and need to be monitored (6).

Diseases, drugs and the *primum movens* COVID-19 are also associated with hyperactive delirium, especially in hospitalized patients with preexisting dementia and cognitive impairment (7).

This syndrome requires a multidisciplinary evaluation balancing cost/effectiveness of therapeutic treatment (sedation or precipitation of respiratory and cardiac failure) and opens a large window of ethical issues, especially in older patients (8).

As suggested by NICE rapid guideline and the Canadian Frailty Network, the assessment of all adults for frailty, irrespective of age and COVID-19 status, is highly recommended especially at hospital admission (6).

As already reported for other diseases, the COVID-19 clinical presentation in older patients is often atypical with less severe symptoms. These subjects both at home and during hospitalization also suffer the isolation and the lack of fundamental support of formal and informal caregivers required for their safety (9).

Despite the peculiar aspects of older patients and the epidemiology of the phenomenon, the geriatric culture and care in COVID-19 wards is often missing. Their application together with additional instruments would be such necessary to facilitate and personalize the clinical approach, not only based on number of diseases but also on functional status of older patient (10).

This narrative review has the specific aim to address different aspects of COVID-19 multi-system

disease starting from diagnostic evaluation, continuing with innovative classification of phases and proposing sequential adapted pharmacological treatment. The document wants also focus on the recovery phase and ethical considerations regarding the risk of limited access of care and accelerated *exitus* in this vulnerable age-category.

Check list of Clinical Symptoms in adult and older persons

The most common symptoms of COVID-19 disease in the adults are represented in Table 1.

This table describes a check-list of more frequent symptoms in adults and would be a guide to orient patients and primary care physicians in assessing older patients with suspected COVID-19 infection. The range of symptoms is similar for COVID-19 and Influenza Infection, although the fraction with severe disease is different. For COVID-19, actual data suggest that 80% of infections are mild or asymptomatic, 15% are severe infections, requiring oxygen and 5% are critical infections, requiring ventilation. These fractions of severe and critical infection would be higher than influenza infection (11, 12).

Symptoms can be traditionally classified into two main groups, including respiratory and gastro-intestinal, and a third group of less organ specific. The quality and severity of symptoms can be different in older persons.

The most common symptoms are fever (98%), cough (77%), dyspnea (63.5%) and muscle/joint soreness (13). The rationale of symptoms distribution across organs is partially explained by the concentration of Angiotensin-Converting Enzyme 2 (ACE-2) virus receptors, which is particularly higher in the lung and lower in the gut. This can explain why less common symptoms include abdominal pain, vomiting and diarrhea and virus might be detected in stool samples although gastro-intestinal transmission remains to be demonstrated (14). It has been also hypothesized that COVID-19 virus can also alter central nervous system directly or alternatively disrupt the gut-barrier permeability and induces the gut-brain link via vagus nerve. This justifies the reduced sense of taste and smell, headache, dizziness and vertigo also observed in COVID-19 patients (15).

Elderly patients, especially with multiple chronic conditions, display less severe and atypical symptoms. The presence of mild symptoms is disproportionate to the severity of their illness (16). They might be afebrile, without cough or sputum production, and show higher prevalence of muscle-joint pain, tachypnea, altered mental status or delirium, unexplained tachycardia and decrease in blood pressure (17). Atypical presentation may be due to several factors, including physiologic changes with age, comorbidities, and inability to provide an accurate history given the constant lack of caregivers during COVID-19 hospitalization (18).

Despite the presence of less severe and atypical symptoms, older patients have a significantly higher mortality. As nicely shown in an elegant retrospective study male sex, time from disease onset to hospitalization, abnormal kidney function, and elevated procalcitonin levels were all significant predictors of increased mortality (14).

Table 1. Check list of Clinical Symptoms in common with adults and specific of older persons.

Gender • M • F	Age • 65-75 • 75-85 • 85-95 • ≥ 95	
Common symptoms		
Fever greater than 37.5° C	• Yes	• No
Dry cough	• Yes	• No
Shortness of breath	• Yes	• No
Fatigue	• Yes	• No
Other symptoms		
Joint and/or muscular pain	• Yes	• No
Headache	• Yes	• No
Nasal congestion	• Yes	• No
Conjunctivitis	• Yes	• No
Runny nose	• Yes	• No
Sore throat	• Yes	• No
Diarrhea	• Yes	• No
Nausea	• Yes	• No
Reduced sense of taste	• Yes	• No
Reduced sense of smell	• Yes	• No
Specific symptoms in older persons		
Confusional state	• Yes	• No
Neurological Features	• Yes	• No

Diagnosis of COVID-19 in adults and evaluation of functional assessment in older patients

Swab and or Lung CT SCAN. The diagnosis of COVID-19 requires the combination of swab and radiologic features. The algorithm initially considers a swab performed with sterile cotton wool suitably rolled around the end of a glass or metal rod, and intended to be swiped on the surface of a natural pharynx and nose cavity. The main nasal swab tests examine the nasopharynx, where the back of the nose meets the top of the throat. This requires a trained hand to perform and some portion of the false negatives arises from improper procedures and poor compliance especially in older adults with acute confusion state (19).

The pharyngeal and nasal swab, once carried out (in some centers not even getting out of the car but with the prior authorization and appointment of the Public Health Office of the Local Healthcare Companies) is sent to an authorized laboratory where the presence of viral RNA or genetic material of the virus is appreciated. In case of positivity, there is the certification that the subject has a COVID-19 infection. But even if done correctly, the swab may produce a negative result. That is because as the disease progresses, the virus passes from the upper to the lower respiratory system.

Importantly, the swab test has a sensitivity of 60-70% and strictly depends on the timing of assessment. This means that in 30-40% of cases, even in the case of a negative buffer, the presence of the Virus cannot be excluded. In these cases, the patient may be asked to try to cough up sputum - mucus from the lower lungs - or doctors may need to take a sample more invasively when a patient is under sedation.

Radiological findings are useful complements in the diagnosis COVID-19 and in the management of one of its most common complications, pneumonia. The most common Computed Tomography (CT) findings of the COVID-19 pneumonia are ground glass and/or consolidation, and mainly reflect the diffuse and bilateral alveolar damage and/or organizing interstitial pneumonia. It has also been reported a strong correlation between the severity of CT pulmonary findings and patients' outcome. Hence, it has been suggested that chest CT could be used as a reliable diagnostic test in the emergency workup of COVID-19, complementing PCR.

A further confirmation of the COVID-19 infection comes from a chest x-ray or even better from a high-resolution chest CT scan (HRCT) which highlights the percentage of lungs and the number of lung lobes affected by the virus. The radiologist, using specific software, processes a visual score or score in percentage. The higher the visual Score the greater the severity of the lung involvement of virus. Visual scores at the time of admission to the hospital of more than 70% are usually associated with a bad prognosis and more than 50% identify a severe disease. Another parameter assessed through the CT scan is the number of lung lobes affected by the infection, which can vary from 0/5 to 5/5. Also in this case, the greater the number of lung lobes involved, the greater the severity of the ongoing lung involvement of virus.

The diagnostic process is the first step of clinical assessment of the patient. Interestingly the initial hypothesis that the COVID-19 is just an infectious disease has been gradually abandoned. An intriguing recent theory suggests that there are different phases in the same disease (Figure 1). The viral disease is limited to phase 1, where an early Infection (8 days of duration) predominates and the host fights to solve the infection. However, if the attempt fails, the activation of an exaggerated response is capable to damage different tissues and organs (kidney, liver, myocardium, brain). Another interesting theory suggests an early endothelial cell damage induced by COVID-19 as common mechanism of vascular impairment across different organs (20).

Three other phases (mainly depicting the host response to virus) are even more important for the clinical course and the outcomes of the patients. More effective will be the host response to virus, more chances the individuals have to survive. Together with clinical evaluation (for instance peripheral capillary oxygen saturation), the functional assessment should also guide clinicians in the admission to Intensive Care Unit (ICU), in selecting therapeutic choices, and in predicting clinical and functional responses. Both UK and Canadian frameworks suggest the usefulness of easy to use instruments such as the Clinical Frailty Scale to assess frailty (10). Other additional

tests include Chair stand test (CST) which is one of the best and validated physical performance tests for older people, and it is reported to be associated with muscle strength of the lower leg. The CST is a simple and feasible physical performance test, even for evaluating older people with limited mobility. Then, many representative cohort studies have demonstrated that the CST is a predictor of disability and falls in older people (21).

Clinical Phases of COVID-19 Infection (Figure 1 and Table 2)

Phase 1. *Infectious–virological Phase or Early Infection Phase 1* (max duration 8 days). The virus is present in the upper airways and digestive tract and usually induces specific symptoms (dry cough, fever, fatigue with normal peripheral oxygen saturation, diarrhea, headache, conjunctivitis) in the adult individuals (13). The body response produces immune (IgM
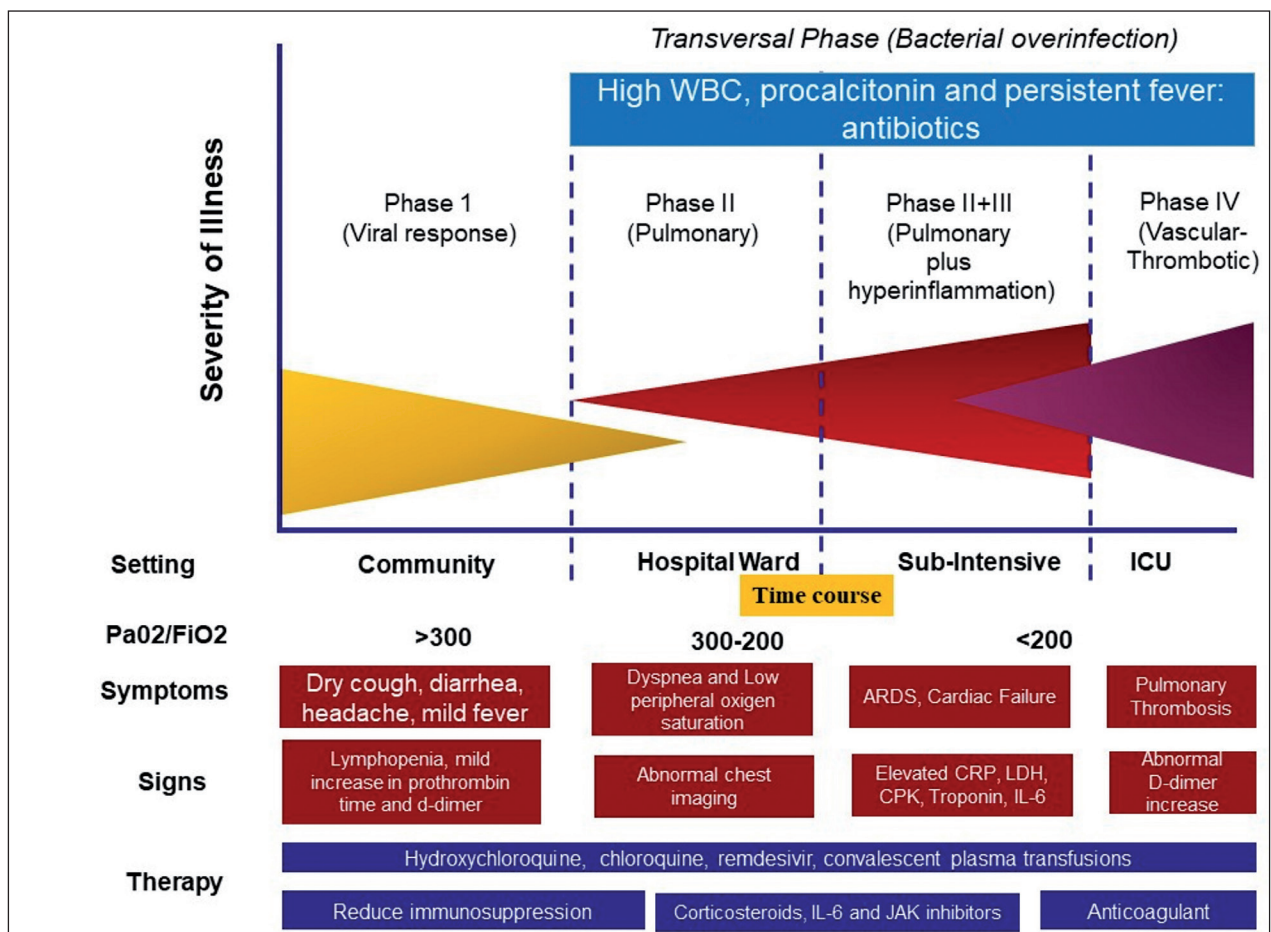

Figure 1. COVID 19 disease across different possible phases, therapeutic strategies and settings.
In Phase 1, viral response predominates and respiratory and gastrointestinal symptoms can be treated at home with hydroxychloroquine and antivirals. *In Phase 2:* pulmonary, fever and dyspnea worsen and rapid diagnosis by CT and hospitalization is required. *In Phase 3,* pulmonary and hyperinflammatory, clinically represented by ARDS, corticosteroids and IL-6 receptor antagonists should be started in sub-intensive wards. *In Phase 4,* thrombotic, anticoagulant therapy should be introduced and admission to ICU indicated. There is a transverse phase: bacterial over infection, typically characterized by high fever, increased white blood cells and procalcitonin, where broad-spectrum antibiotic therapy is the choice treatment.
Legend of Figure: WBC: White Blood Cells, ICU: Intensive Care Unit, Pa02: Partial Pressure of Oxygen, FiO2: Inspired Oxygen Fraction, ARDS: Acute Respiratory Distress Syndrome, CRP: C-Reactive Protein, LDH: Lactate Dehydrogenase, CPK: Creatine Phosphokinase, IL-6: Interleukin 6, JAK: Janus Kinase

Table 2. Biomarkers of different Phases during Covid-19 Infection.

	Phase 1 **Infection**	Phase 2 **Pulmonary**	Phase 3 **Pulmonary plus Inflammatory**	Phase 4 **Vascular/Thrombotic**
WBC	Low	Normal	Normal	Normal
CRP	Middle High	Really High	Really High	Really High
Procalcitonin	Normal	Normal	Normal	Normal
D-Dimer	Normal	Normal	Middle High	Really High
Troponin I hs	Normal	Middle High	Middle High	High
Transversal Phase or Phase 5: High Procalcitonin and WBC				

antibodies) and inflammatory reactions (Interleukin-6 and other inflammatory cytokines). Both responses, especially if supported by appropriate pharmacological treatment, translate into an infective resolution in 80% of cases. The different response in older patients and in different categories (fit, frail, disable) is an interesting topic to be investigated (12).

The phase 1 treatment includes drugs with mixed anti-viral and anti-inflammatory activity (hydroxychloroquine) and antibacterial drug with minimal anti-viral action (azithromycin) (14, 17). These drugs act synergistically on heart rhythm and require, because of the frequent concomitant use and especially in subjects with previous cardiac disease, electrocardiogram (EKG) trace to monitor QTc interval (22). Low molecular weight heparin, in the presence of good renal and liver function, at prophylaxis doses is also suggested (23). In older patients, these specific aspects require additional and careful evaluation given the inadequate formulas currently used to assess for instance renal function (24). In about 80% of cases, the disease ends at this stage and can be managed at home.

However, the onset and persistence of symptoms within 2-3 days requires an immediate communication to primary care physician (or general practitioner) for a timely diagnosis and therapy. Pharmacological treatment must be accompanied by the adoption of home behavioral measures in order to avoid contagion of the other family members. If the fever is persistently higher ≥38°C, especially for more than 3-4 days, or if peripheral oxygen saturation drops below 95% and/or dyspnea increases, we should suspect an exaggerated inflammatory response and the extension to the lung and recommend the hospitalization. The typical serum biomarker picture of this phase could be represented

by low WBC, CRP and D-dimer mildly increased, normal troponin I hs levels (Table 2).

Phase 2. *Pulmonary or Proliferative Phase 2.* This phase usually occurs after 10 days on average from the onset of symptoms in which the virus migrates to the lower respiratory tract lung. Characterizing symptoms lasting 5 days or longer, range from shortness of breath to severe dyspnea and fatigue. This phase can be characterized by low peripheral oxygen saturation (SpO2 <95%). Endothelial and initial cardiac damage are also possible (25). At this stage, hospitalization in semi-intensive wards could be necessary. Acute Confusional State in older persons is frequently observed and sedative and palliative treatment are important and detrimental confounders. Men experience more clinical complications than women. This different exposure can be explained by higher expression pattern of ACE2 receptors in adult human testes at the level of single-cell transcriptome suggesting that this organ is a potential target of SARS-CoV-2 infection, and one of the reasons for the rapidly spreading disease (26). The typical serum biomarker picture of this phase could be represented by normal WBC, further increase in CRP and D-dimer levels, troponin I hs levels that require to be monitored for the potential involvement of myocardium and pericardium (Table 2).

Phase 3. *Pulmonary-Hyper-Inflammatory Phase 3*, which is characterized by systemic symptoms with multi-organ involvement (ARDS SIRS/ Shock Cardiac Failure) (27, 28). Individualized treatment in this phase is required, considering for example corticosteroids (Methylprednisolone 1 mg/Kg/day or dexamethasone at 20 mg/day intravenously), human immunoglobulin, inhibitors of the IL-6, IL-2, and JAK2 receptor. This phase requires hospitalization in ICUs

or respiratory intensive care unit (29). The typical bio-marker picture of this phase could reproduce phase 2 (Table 2).

Phase 4. Vasculitic-Thrombotic *Phase 4* (coexisting or immediately following the previous phase) consists of endothelial damage, local and diffuse thrombotic phenomena and pulmonary hypertension (30). There is the rationale, especially in this phase, to support, at high dosages, and based on weight and renal function, the use of enoxaparin, very known also for its antiviral activity (31, 32).

The presence of pulmonary hypertension suggests also the potential usefulness of phosphodiesterase inhibitors releasing nitric oxide such as sildenafil (33). The typical serum biomarker picture of this phase could be represented by normal WBC, very-high levels of D-dimer and troponin I hs levels that require to be monitored for the potential occurrence of thrombotic events in different organs (Table 2).

The separation of different phases of disease contributes to delineate a specific timing for starting appropriate pharmacological treatment and establishing setting (home and hospital wards) at increased intensity of care. In case of persistent fever, higher than 37.5°C for a time longer than 3 days and peripheral oxygen level lower than 95% after starting therapy, we should consider and proceed to hospitalization especially in multimorbid older patients with cardiac, respiratory diseases and diabetes.

The use of antivirals is poorly supported by randomized controlled clinical trials performed only in adult patients (34) and should be limited to the initial phase of the disease. Antivirals are poorly indicated during phase 2 (35), and not indicated at all during phases 3 and 4. Vice-versa, the anti-inflammatory-immunosuppressive therapy, are contraindicated during phases 1 and 2 in which the organism/host is elaborating or implementing its defensive strategy. Corticosteroids and other anti-inflammatory medications should be also carried-out, once having careful evaluated specific contraindications, during phases 3 and 4, where the combination anti-inflammatory/ anticoagulant therapy is suggested in case of significant increase of d-dimer and/or positive pulmonary CT with contrast.

Late phases are usually characterized by exaggerated phase response of the host which is harmful to the host and needs to be attenuated (28, 36). This might be particularly detrimental in older patients where a chronic inflammatory status is often present.

Every single phase of the pathology is also influenced by the undergoing pharmacological treatment and related side effects. Drug-drug interaction deserves particular attention especially in older persons with polypharmacy. All these medications may induce gastro-intestinal symptoms (especially diarrhea) and worsen kidney and liver function. The EKG at the basal entry should be carried out on regular basis to monitor the QTc interval and to exclude the potential myocardial and pericardial damage induced by the infectious process.

Insights and evidence of the treatment according to different clinical phases of the COVID-19 infection

Treatment of the phase 1 COVID-19 infection

Treatment in this phase, usually lasting about 7-8 days, consists of drugs with anti-inflammatory activities. These drugs, such as chloroquine or hydroxychloroquine should be started as soon as possible (37). However, their utilization is actually based on *in vitro data* (38, 39) and single open label non-randomized trial conducted in 36 patients with COVID-19 (40).

Antiviral drugs derive their use from trials verifying their effective treatment of other viruses including SARS (Severe Acute Respiratory Syndrome-related coronavirus) and MERS (Middle East Respiratory Syndrome coronavirus). In particular, preliminary genomic studies on 2019-nCov showed that the sequence has similarities with the corresponding SARS and MERS enzymes, and this justifies why repurposing exiting SARS and MERS inhibitors for 2019-nCOV (14).

Although the use of many anti-viral drugs has been proposed, particular attention received lopinavir/ritonavir and remdesivir. The first antiviral drug, lopinavir/ritonavir, has specific indication for treat HIV and was also utilized in the 2003 for SARS. Convincing evidence of its therapeutic effects on COVID-19 is lacking. Moreover, a recent randomized clinical trial found no different clinical effect compared to standard care on 2019-nCov infection. Only in the modified intention-to-treat analysis, which excluded three pa-

tients with early death, the between-group difference in the median time to clinical improvement (median, 15 days vs. 16 days) was significant, albeit modest (34).

Another virally targeted agent is the remdesivir, a very promising drug, which is a drug currently being investigated as a potential COVID-19 treatment through several clinical trials. In details, two phase III randomized, placebo-controlled double-blind, multicenter trials were initiated in early February to investigate remdesivir in two different dosages 200 mg/day and 100 mg/day for 9 days with estimated complete results at the end of April 2020 (41).

Finally, the favipiravir, an antiviral drug manufactured by Japanese pharmaceutical company Fujifilm Toyama Chemical, was approved for treatment of novel influenza on February 15, 2020 in China, and clinical trials testing this medication are undergoing. Preliminary data from 80 patients indicated that favipiravir had more potent antiviral effect than lopinavir/ritonavir and even with lower side-effects (42).

However, given that no current definitive specific treatment for COVID-19 infection has been proved based on randomized clinical trial, WHO has now launched the SOLIDARITY trial to investigate four potential treatments: remdesivir, chloroquine/hydroxychloroquine; lopinavir and ritonavir; and lopinavir and ritonavir plus interferon-β.1 The only limitation of this study is that will not be double blind, but it will include thousands of patients from several countries (43).

Treatment of the phase 2 (Pulmonary) COVID-19 infection

This phase normally is associated in the adults with the presence of persistent high fever. This symptom often requires admission to Emergency Department and hospitalization for the execution of pulmonary CT scan. This technique is the gold standard for the diagnosis of typical interstitial pneumonia.

The most important observation of this infection phase is the rapid progression into pulmonary impairment with a rapid worsening hypoxia. Therefore, patients who failed to standard oxygen therapy required an advanced oxygen/ventilatory.

Patients may also have increased work of breathing, demanding positive pressure breathing assistance, which could be guaranteed by non-invasive ventilation (including continuous positive airway pressure [CPAP] or bi-level positive airway pressure [BiPAP]) in patients with hypoxemic respiratory failure. Prone ventilation in patients with persistent severe hypoxic failure should be considered.

Finally, patients who are acutely deteriorating undergo intubation and mechanical ventilation. Two thirds of patients who required critical care in the UK had mechanical ventilation within 24 hours of admission (44).

In this phase, the presence of elevated serum levels of inflammatory cytokines, such as IL-6 could induce pulmonary damage or proliferative pulmonary phase. IL-6 receptor antagonists (e.g., tocilizumab, sarilumab, siltuximab) can be used. In particular, the tocilizumab which is a monoclonal antibody that blocks the IL-6 signalling pathway is currently used to treat rheumatoid arthritis. However, given the limited evidence on the safety or efficacy of the drug in clinical treatment of COVID-19, the FDA launched through a double blind, a randomised phase III clinical trial as a treatment for severe covid-19 pneumonia with tocilizumab in combination with standard of care (44).

Treatment of the phase 3 (Pulmonary and inflammatory) COVID-19 infection

Acute respiratory distress syndrome (ARDS) is an acute, diffuse, inflammatory form of lung injury related with high mortality. Diagnostic criteria (Berlin definition 2012) include non-cardiogenic respiratory failure, with respiratory symptoms, bilateral opacities on CT scan and presence of a moderate to severe impairment of oxygenation (45, 46). The PaO2/FiO2 defines the severity of the ARDS (calculated data with a positive end-expiratory pressure (PEEP) or continuous positive airway pressure (CPAP) ≥5 cm H2O) in the absence of cardiac failure or fluid overload.

- Mild ARDS – PaO2/FiO2 is >200 mmHg, but ≤300 mmHg.
- Moderate ARDS – PaO2/FiO2 is >100 mmHg, but ≤200 mmHg.
- Severe ARDS – The PaO2/FiO2 is ≤100 mmHg (47).

Excessive inflammatory response is an essential characteristic of ARDS pathophysiology, with an increase of Interleukin-1 Beta (IL-1β), Interleukin-2 (IL-

2), IL-6, Interleukin-17 (IL-17), Interleukin-8 (IL-8), Tumor Necrosis Factor-α (TNF-α) and C-C Motif Chemokine Ligand 2 (CCL2) (48). It is known that in patients with ARDS, elevated plasma IL-6 at baseline predict a poor survival (28). Also in COVID-19 patients, higher IL-6 levels are associated with an increased risk of hospitalization and other negative outcomes (49). At this stage of the disease, patients typically show dyspnea, tachypnea, fever and tachycardia. They can also show severe, acute confusion (especially in older persons), respiratory distress and cyanosis.

As lung dysfunction progresses, it is necessary to increase oxygen-therapy until non-invasive mechanical ventilation is required (50, 51). The use of corticosteroids could be beneficial to modulate the excessive immune response, but their use is controversial. A recent study shows that the use of corticosteroids in ARDS reduced all-cause mortality and duration of mechanical ventilation, and increased ventilator-free days (52). In this regard, we hypothesized that patients already taking corticosteroids for other diseases, such asthma, pulmonary fibrosis, rheumatologic diseases and without indication for bacterial over-infections, can take advantage from adequate dosages of corticosteroids. However, future clinical trials are required to verify these aspects.

In this phase, convalescent plasma from patients who have recovered from viral infections can be used as a treatment. Clinical trials to determine the safety and efficacy of convalescent plasma that contains antibodies to SARS-CoV-2 in patients with COVID-19 have started. A small preliminary case-series of five critically ill patients reported clinical improvement after convalescent plasma transfusions (53). Another study of 10 patients with severe illness in China noted symptomatic improvement within 3 days. Viral load was undetectable within 7 days in 70% of patients. No serious adverse reaction was noted.

Treatment of the phase 4 (Vascular-Thrombotic) COV-ID-19 infection

COVID-19 and ARDS can evolve into thrombotic phenomena. Prolonged inflammation is responsible for a pro-coagulation state, with activation of the endothelial vasoconstrictors and formation of lung micro thrombi, also found during autoptic examination

(52, 54, 55). Intriguingly, SARS-CoV-2 can directly infect engineered human blood vessel organoids in vitro. Very recent case-series in patients with COVID-19 have demonstrated an endothelial cell involvement across vascular beds of different organs especially in those with preexisting thrombotic disease (32, 56). For all these reasons, a vasculitic/thrombotic phase can be hypothesized during COVID ARDS. Clinically, episodes of intense dyspnea and respiratory distress may occur. Fever can be resolved. The pro-coagulant state is characterized by an increase in the D-dimer, which must therefore be regularly analyzed (28). In details, if D-dimer level, normally performed every three days, increase more than 6 times from admission to later check, this parameter represents a good index for identifying high-risk groups of Venous thromboembolism and anticoagulant treatment, if not contraindicated, should be prescribed (57). Respiratory distress syndrome (ARDS) is a common complication of COVID-19 infection. Ozoline and colleagues demonstrated that in patients with ARDS higher plasma concentrations of tissue factor and plasminogen activator inhibitor-1 were present at day seven compared to non-ARDS (58). The mechanisms contributing to this lung coagulopathy are localized tissue factor-mediated thrombin generation, and depression of broncho-alveolar plasminogen activator-mediated fibrinolysis, mediated by the PAI-1 increase (59). Thus, treatment with heparin might be helpful in mitigating this pulmonary coagulopathy. Moreover, adjunctive treatment with Low-Molecular-Weight Heparin (LMWH) within the initial seven-day onset of ARDS reduces the risk of 7-day mortality by 48% with a meaningful improvement of the PaO2/FiO2 ratio (31). In the same study, the risk of 28-day mortality was reduced by 37% as well. In a report from a Wuhan University hospital, heparin use was associated with lower mortality in patients with Sepsis-Induced-Coagulopathy (SIC) score ≥4 (40.0% vs 64.2%, P=0.029), but not in those with SIC score <4 (29.0% vs 22.6%, P=0.419). In the same report patients with D-dimer > 3.0 ug/mL experienced a 20% mortality reduction after heparin treatment (32.8% vs 52.4%, P=0.017) (57).

Another fascinating concept is the antiviral role of heparin which has been studied in experimental models. Given its polyanionic nature, heparin can bind

to several proteins and thus act as effective inhibitors of viral attachment (60). One example is in herpes simplex virus infections. Heparin competes with the virus for host cell surface glycoproteins inhibiting the virus entrance in the cells. Also, in zika virus infection, it prevents virus-induced cell death (61). Finally, the use of heparin at a concentration of 100 μg/mL halved the infection in an experimental model of cells injected with sputum from a patient with SARS-associated CoV pneumonia (62). However, the clinical benefits in any of these viral infections are yet to be determined.

Moreover, heparin may also be helpful in microvascular dysfunction and this is of importance given the well-known role of endothelial dysfunction in the cardiac failure, another increasingly recognized complication of COVID-19.

Finally, a recent document of the Italian national drugs agency (63) advices to consider the use of LMWH in serious cases of COVID-19 (defined by the presence of one of the following conditions: PaO2/FiO2 < 300, respiratory rate > 30/min and SpO2< 93% at rest) when the D-dimer is markedly increased (4-6 fold) and the SIC score is > 4 (Table 2) and myocardial infarction or other thrombotic events cannot be excluded. However, high rate of high incidence of venous thromboembolic events may occur in severe COVID-19 patients, irrespective of anticoagulation (64).

Transversal phase or over-infection phase (Phase V)

All previous phases of the COVID-infection can be complicated by the presence of bacterial over-infection. This condition should be suspected when specific serum biomarkers such as WBC and procalcitonin are pathologically elevated (Table 2) (65). In this case, specific antibiotic therapy should be promptly prescribed, even in accordance with suggested guidelines (66).

Polypharmacy in older persons: interaction of drugs utilized during acute disease in older persons with COVID-19

Polypharmacy is one of the main characteristics in older subjects. There is an increased risk of adverse events in this specific age-group. Although there are no Food and Drug Administration (FDA)-approved drugs to prevent or treat COVID-19, nevertheless pre-liminary clinical research, based on in vitro-data, have suggested the use of pharmacologic agents as chloroquine or hydroxychloroquine, azithromycin, lopinavir/ritonavir and other anti-retrovirals (67). Some of these drugs may increase risk of QT prolongation, ventricular proarrhythmia and sudden cardiac death. Some of the current COVID-19 repurposed drugs have known risk of US Food and drug administration Adverse Event Reporting System (FAERS), long QT syndrome and torsade de points (TdP) and cardiac arrest for azithromycin, and hydroxychloroquine, and possible risk for lopinavir/ritonavir.

In the prevention of QTc-prolongation, special attention should go to high-risk patients. Age is one of the main determinants of this risk score which has been derived and validated by Tisdale et al. (68), for prediction of drug-associated QT prolongation among cardiac-care-unit-hospitalized patients. The application of this scale identifies Maximum Risk Score of 21 and three different classes of risk, low (score ≤ 6 points), moderate (7-10 points) and high (≥ 11 points) (Table 3) (69).

The goal of QTc screening in this setting is not to identify patients whom are not candidates for therapy, but to identify those who are at increased risk for TdP in order that aggressive countermeasures may be implemented.
1. Baseline
    a. Discontinue and avoid all other non-critical QT prolonging agents.
    b. Assess a baseline ECG, renal function, hepatic function, serum potassium and serum magnesium.
    c. When possible, have an experienced cardiologist/electrophysiologist measure QTc, and seek pharmacist input in the setting of acute renal or hepatic failure.
2. Relative contraindications (subject to modification based on potential benefits of therapy)
    a. History of long QT syndrome, or
    b. Baseline QTc >500 msec (or >530-550 msec in patients with QRS greater than >120 msec)
3. Ongoing monitoring, dose adjustment and drug discontinuation
    a. Place on telemetry prior to start of therapy.
    b. Monitor and optimize serum potassium daily.

c. Acquire an ECG 2-3 hours after the second dose of hydroxychloroquine, and daily thereafter.

d. If QTc increases by >60 msec or absolute QTc >500 msec (or >530-550 msec if QRS >120 msec), discontinue azithromycin (if used) and/or reduce dose of hydroxychloroquine and repeat ECG daily.

e. If QTc remains increased >60 msec and/or absolute QTc >500 msec (or >530-550 msec if QRS >120 msec), reevaluate the risk/benefit of ongoing therapy, consider consultation with an electrophysiologist, and consider discontinuation of hydroxychloroquine (70).

During COVID-19 infection adult and older patients may also experience a higher incidence of gastrointestinal symptoms including diarrhea. The ongoing treatment with antivirals and anti-inflammatory could worsen this symptomatology, increasing potassium and magnesium deficiency and amplifying the risk already described of cardiac events and arrhythmia. In older patients it is widely observed the chronic, not always appropriate, use of proton pump inhibitors (PPI). One year PPI treatment has been associated with increased risk of all-cause mortality (71). Authors suggest that magnesium deficiency, clostridium difficile infection and Intestinal Colonization with Multidrug-Resistant Microorganisms might justify the link between inappropriate use of PPI and mortality (72-74). Interestingly their chronic use has been associated with malnutrition and functional decline (75, 76), two main

Table 3. Risk Score for identifying Drug-Associated QTc Prolongation.*

Risk Factors	Points
Age ≥68 y	1
Female sex	1
Loop diuretic Use	1
Serum Potassium ≤3.5 mEq/L	2
Admission QTc ≥450 ms	2
Acute Myocardial Infarction	2
≥2 QTc-prolonging drugs	3
Sepsis	3
Heart failure	3
One QTc-prolonging drug	3

* A cut-off ≥ 7 can be used to assess moderate-severe risk. Modified by reference 69.

aspects to be assessed and monitored in older patients with COVID-19 infection.

The role of nutrition and exercise in favoring recovery during the post-discharge phase in older persons

Older age and the presence of multimorbidity are almost invariably associated with impaired nutritional status and sarcopenia (77). Some studies have demonstrated that hospitalization and associated bed rest even for short time-period (20 days) promote detrimental reduction in muscle mass, strength and physical function, with altered aerobic exercise capacity (78,79).

COVID-19 also amplifies these symptoms if we consider that muscle pain and fatigue are frequent symptoms also in older persons. The bed rest and high inflammatory and hypercatabolic status following COVID-19 infection can promote a further reduction in walking speed, stair ascent power and chair stand test. These functional parameters, as well as the loss of strength, may compromise the recovery of functional skills in the elderly and induce the loss of autonomy. Although albumin and prealbumin circulating levels should not be considered as nutritional markers in patients with acute inflammatory response, studies have shown an association between low prealbumin levels and increased risk of respiratory failure with increased need for mechanical ventilation (80).

All infected patients at hospital admission, especially those at nutritional risk should undergo nutritional assessment and receive nutritional support as early as possible. There is evidence that nutritional derangements should be systematically and urgently managed in patients affected by COVID-19, also considering that the immune response is weakened by inadequate nutrition. Nutritional intervention should be complementary to pharmacological treatment and the presence of a standardized protocol would be extremely helpful. For example, in Italy, a nutritional protocol has been developed and proposed by University of Milan and Pavia in Lumbardy which is one of the main Italian regions affected by the Italian COVID-19 crisis (81).

This is based on systematic supplementation of certain nutrients (e.g. vit. D, whey proteins and omega 3 fatty acids) with anabolic and anti-inflammatory activity, oligo-elements stimulating immune system and particularly indicated in this high systemic inflamma-

tory and catabolic condition. Obesity can be considered a specific type of malnutrition, where the excess of macronutrients intake could also be accompanied by micronutrients deficiency (82).

The Centers for Disease Control and Prevention considers those with BMI ≥ 40 kg/m^2 as being at risk for flu complications. During the 2009 H1N1 pandemic, obesity was recognized as an independent risk factor for complications from influenza (80).

It is now well accepted that obesity increases one's risk of being hospitalized with, and dying from, an influenza virus infection, and it can be considered a predictor for poor outcome during COVID-19 infections (83). It has been reported that the presence of obesity in a group of metabolic associated fatty liver disease (MAFLD) patients was associated with a ~ 6-fold increased risk of severe COVID-19 illness (unadjusted-OR 5.77, 95% CI 1.19-27.91, p=.029). Given the high prevalence of obesity and overweight in European countries (30-70%), the challenge for virus pandemics is therefore to protect these subjects (84). Although the effects of COVID-19 on patients with obesity have not yet been well-described, it is well known the impact of H1N1 influenza the care of patients with obesity and with severe obesity, due to its adverse effect on pulmonary function (85). The increased morbidity associated with obesity in COVID-19 infections may be explained by increased inflammatory cytokines, other important determinants of severity infection include basal hormone milieu, defective response of both innate and adaptive immune system and sedentariness. It has been suggested by recent evidences that a large obese population increases the chance of appearance of more virulent viral strain, prolongs the virus shedding throughout the total population and eventually may increase overall mortality rate of an influenza pandemic (86). Finally, some authors outlined a framework whereby adipose tissue may be as a reservoir for more extensive viral spread with increased shedding, immune activation and cytokine amplification (83).

Even, there are no specific studies on nutrition management in COVID-19 infection, ESPEN promotes considerations based on the best of knowledge and clinical experience.

First, patients at risk for poor outcomes and higher mortality following infection with SARS-CoV-2, namely older adults and multimorbid individuals, should be checked for malnutrition through screening and assessment. Criteria can be used are the MUST criteria or, for hospitalized patients, the NRS-2002 criteria. Recently it has been introduced the GLIM (Global Leadership Initiative on Malnutrition) criteria for malnutrition diagnosis. Obese individuals should be screened and investigated according to the same criteria, as they are malnourished. In a recent review about potential interventions for novel coronavirus based on the Chinese experience authors suggested that the nutritional status of each infected patient should be evaluated before the administration of general treatments (87).

Subjects with malnutrition should optimize their nutritional status, ideally by diet counseling from an experienced professional. Macronutrients intake proposed by ESPEN are the following.

Energy needs can be assessed or predicted by equations or weight-based formulae such as:

- 27 kcal per kg body weight and day; total energy expenditure for polymorbid patients aged >65 years;
- 30 kcal per kg body weight and day; total energy expenditure for severely underweight polymorbid patients*;
- 30 kcal per kg body weight and day; guiding value for energy intake in older persons, this value should be individually adjusted with regard to nutritional status, physical activity level, disease status and tolerance.

*The target of 30 kcal/kg body weight in severely underweight patients should be cautiously and slowly achieved, as this is a population at high risk of refeeding syndrome.

Protein needs are usually estimated using formulae such as:

- 1 g protein per kg body weight and day in older persons; the amount should be individually adjusted with regard to nutritional status, physical activity level, disease status and tolerance.
- ≥ 1 g protein per kg body weight and day in polymorbid medical inpatients in order to prevent body weight loss, reduce the risk of complications and hospital readmission and improve functional outcome.

Fat and carbohydrate needs are adapted to the energy needs while considering an energy ratio from fat and

carbohydrates between 30:70 (subjects with no respiratory deficiency) to 50:50 (ventilated patients) percent.

Also micronutrients, such as vitamins and minerals, should be ensured to potentially reduce disease negative impact, by supplementation and/or adequate provision. Low levels or intakes of micronutrients such as vitamins A, E, B6 and B12, Zn and Se have been associated with adverse clinical outcomes during viral infections (86). Recently, a Chinese review (88) proposed that also vitamin C, omega-3 polyunsaturated fatty acids, as well as selenium, zinc and iron should be considered in the assessment of micronutrients in COVID-19 patients.

Oral nutritional supplements (ONS) should be used whenever possible to meet patient's needs, when dietary counseling is not sufficient to reach nutritional goals. Individuals infected with SARS-Cov-2 outside of the ICU should therefore be treated to prevent or improve malnutrition. The oral route is always preferred when practicable. Nutritional treatment should start early during hospitalization (within 24-48 h) and targets should be met gradually to prevent refeeding syndrome. ONS provide energy-dense alternatives to regular meals and may be specifically enriched to meet targets in terms of protein as well as micronutrients (vitamins and trace elements). The daily estimated requirements of these nutrients should be regularly provided. Nutritional treatment should continue after hospital discharge with ONS and individualized nutritional plans; this is particularly important since pre-existing nutritional risk factors continue to apply and acute disease and hospitalization are likely to worsen the risk or condition of malnutrition.

According to ESPEN statements, in multimorbid inpatients and in older persons with reasonable prognosis, when nutritional requirements cannot be met by the oral route, enteral nutrition (EN) should be preferred to parenteral nutrition (PN), because of a lower risk of complications (related or not related to infectious). PN should not be started until all strategies to maximize EN tolerance have been attempted.

About the nutritional management of COVID-19 patients admitted to intensive care units, ESPEN Guidelines on this specific topic are available giving suggestions on different stages of treatment according to patients' condition and respiration. Infected patients not intubated who do not reach nutritional requirements by normal diet, first should be supplemented by ONS, then EN treatment can be considered. When limitations are present to EN, PN can be prescribed.

In COVID-19 intubated and ventilated ICU patients, enteral nutrition (EN) should be started through a nasogastric tube; post-pyloric feeding should be performed in patients with gastric intolerance after prokinetic treatment or in patients at high-risk for aspiration; the prone position per se does not represent a limitation or contraindication for EN.

Patients' energy expenditure can be derived from ventilator (VO2, oxygen consumption from pulmonary arterial catheter or VCO2, carbon dioxide production), and energy is administered according to its value. Hypocaloric nutrition (not exceeding 70% of EE) should be administered in the early phase of acute illness with increments up to 80 and 100% after DAY 3. Regarding protein intake, 1.3 g/kg protein equivalents per day can be delivered progressively. In obese subjects, 1.3 g/kg "adjusted body weight" protein equivalents per day is recommended. Adjusted body weight is calculated as ideal body weight + (actual body weight - ideal body weight) * 0.33.

After mechanical ventilation, patients may present swallowing difficulties and texture-adapted food can be considered after extubation. If swallowing is proven unsafe, EN should be administered. In cases with a very high aspiration risk, post-pyloric EN or, if not possible, temporary PN during swallowing training with removed naso-enteral tube can be performed.

Hydration status of patients should be considered and assessed after the acute and critical phases. High grade of inflammation and infectious status with long lasting fever period may cause dehydration which needs to be treated before discharge.

Furthermore, some patients with COVID-19 show intestinal disease, thus nutritional and gastrointestinal function should be assessed for all patients. Some authors suggest that nutritional support and application of prebiotics or probiotics should be suggested to regulate the balance of intestinal microbiota and reduce the risk of secondary infection due to bacterial translocation (89).

Almost no information is available on metabolic and nutritional needs of ICU survivors, and known

nutritional practices reveal a poor nutritional performance during ICU stay and after discharge. A few evidences showed that currently poor nutritional practices are adopted for older patients who leave the ICU in the ward, and further research are needed to fill the gap. Following hospital discharge, especially patients should comply with high-protein targets either by prolonged tube feeding or by enhanced high-protein oral nutrition (supplement) intake. Further, nutritional and metabolic therapies such as anabolic/anti-catabolic agents in the recovery need urgent studies (90).

Nutritional intervention should be combined (whether possible) with physical exercise in order to optimize its anabolic effect (91). Different phases and week programs could be also followed with the specific aim of recovering physical and motor skills (Table 4).

Phase 1. Recover of orthostatism. Once the acute phase has been resolved, the multidomain intervention should include exercise and target the recovery of orthostatic and motor skills. It would be important progressively increase the anti-gravity position starting from the sitting position on the bed with slow exercises and movements to be repeated several times a day, until the complete recovery of the upright position.

Phase 2. Train balance and coordination of movements. Following this first phase, static and dynamic balance exercise should be performed for improving balance impairment. Holding on the back of a chair, stand on tiptoe and then return to the starting position, or keep the balance in monopodalic support.

Phase 3. Regain muscle strength. Low intensity muscle strengthening exercises might be useful for recovering strength and functional autonomy, improving stability, balance and reducing the risk of falls. For example, sitting back on a chair, slowly raise left leg until it is fully extended, pause for a breath, then slowly lower left leg back to the ground. This sequence should be repeated 10 times both sides.

Phase 4. Start endurance training. Aerobic exercise, like walking inside the house or stationary bike, can be started after the regaining of motor skills and strength, initially 10 minutes of activity then up to 20 minutes.

Maintenance: individual multicomponent exercise program. At the end of the total recovery, a multicomponent exercise program can include aerobic, resistance, balance, coordination and mobility training exercises (92). Twenty minutes of aerobic exercise every day and three days a week of resistance exercises at low and medium intensity should be the ideal choice for older people to enhance the protective role of physical activity (93-95).

Conclusive remarks

The pathophysiology of the COVID-19 infection especially in older adults requires a dynamic process

Table 4. Weekly exercise program for fit and frail older persons during Recovery Phase from COVID-19.

	Type of exercise			
DAY	Aerobic excise stationary bike, walking, dance	Balance	Resistance	Stretching/ mobility
Monday	20 minutes	--	4/5 resistance exercises for arms and legs	Mobility training exercises
Tuesday	20 minutes	2/3 Balance and coordination exercises	--	--
Wednesday	20 minutes	--	4/5 resistance exercises for arms and legs	Stretching exercises
Thursday	20 minutes	2/3 Balance and coordination exercises	--	--
Friday	20 minutes	--	4/5 resistance exercises for arms and legs	Mobility training exercises
Saturday	20 minutes	--	--	--
Sunday	20 minutes	2/3 Balance and coordination exercises	--	--

with important clinical and ethical implications in the hospital and community care.

Now it is quite clear that the infection produces a systemic disease with different phases at increasing severity of symptoms. Older patients infected by COVID-19 often experience atypical and less severe symptoms in older persons, side-effects of the drugs and require specific nutritional and motor treatment for avoiding disability and death.

By expanding the proposal of Hasan K et al. (96), we added to the already known infective, pulmonary and inflammatory, a potential IV phase for emphasizing the presence of a vascular-thrombotic process more frequent during the severe pulmonary disease. We also underlined the bacterial over-infection, which can be transversally present in all phases and requires the need of antibiotic treatment. As addressed by Italian Ethics Committee it is ethically unacceptable, each selective care criterium based on «age, gender, condition and social role……and disability». These principles have been often ignored, especially in older COVID-19 patients. Examples reported from the sociologist Giuseppe De Rita and coming from UK or Holland, describe that patients 70 year or older are invited to sign a declaration where they refuse to be cured if another younger patient requires the same treatment.

A statement signed on March 23rd 2020 by the European Geriatric Medicine Society (EUGMS)

(97) suggests that advanced age should not by itself be a criterion for excluding patients from specialized hospital units and care. Simplified models of comprehensive geriatric assessment and tailored interventions (including evaluation of frailty, hydration and nutritional with Body Mass Index and CST, Social and Psychological support, management of polypharmacy) are mandatory to guide appropriate clinical approaches, especially if older subjects are really fit, without any cognitive and motoric dysfunction, and to improve the patient's quality of life (98). These principles should be applied to every setting of care including Community/Primary Care, Hospital and Nursing Home placement.

Innovative organizing multidisciplinary models are especially important during the transition care and Coronavirus outbreak, because older people might experience an understandable slowing down of physi-

cal and mental capacities in the discharge from acute care with prolonged hospital stays and increased risk of iatrogenic consequences. All the necessary efforts should be made to consider more intermediate care and home care facilities to improve rehabilitation and recovery of older patients.

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