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Review Article

Proposal of Triages for SARS-Cov-2 Infected People Outside and Inside Hospital

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Abstract

The Covid-19 pandemic has propagated rapidly in a short period of time with considerable morbidity and mortality rates. The majority of health services have been disrupted by shortages, which have compromised the quality of care provided in many hospital facilities. Infected symptomatic individuals, mainly present respiratory system failure, however, other systems may also become affected. With the aim of facilitating the standardization of care we propose two different triage models, Covid-19 Triage-1 and Covid-19 Triage-2, to be used outside and inside a hospital setting, respectively. It is expected that the wider application of these triages will allow a better evaluation of patients` clinical status and their response to therapeutic interventions, along with an optimal use of the available health resources. In addition, they may be useful tools for the comparison of data and the design of future studies.

Keywords: Coronavirus infection; Covid-19; Pandemia; SARS-Cov-2; Triage

Introduction

The infection caused by the coronavirus SARS-CoV-2, known as Covid-19, has shown high infectivity propagating rapidly across all continents in a short period of time with considerable morbidity and mortality. Most of the infected people, roughly 80%, are asymptomatic or show mild respiratory symptoms; however, it has been reported that approximately 15% of them exhibit more severe clinical picture and almost 5% fall critically ill with a severe inflammatory response, respiratory and multiorgan failure, needing admission to an Intensive Care Unit (ICU) and mechanical ventilation [1]. The differences in response may depend on the degree of viral load, host immune response, age of patients and presence of comorbidities.

Patients infected by the SARS-CoV-2 virus, like other diseases associated with the coronavirus family, when symptomatic, mainly present with respiratory failure. Owing to the rapidly evolving global outbreak, the majority of health services have been caught by shortages in hospital space, particularly in critical care, insufficient number of ventilators and other life support measures, that together with a dearth of personnel and protective equipment, have resulted in suboptimal clinical management of patients at times. In some cases, the demand for critical care beds and the lack of sufficient ventilators, have forced hard decisions, such as denying patients treatment to make resources available for other patients with a better probability of survival, [2] and protocols have been developed for the rationing and reallocation of ventilators [3,4]. Hence, it is clear that, for a safe handling of patients and an optimum use of health resources, it is necessary to triage patients to make an accurate assessment of their clinical status, enabling the identification of those that may develop complications and requiring advanced treatments.

Therefore, here we propose the use two different triage models for patients affected by SARS-CoV-2 with the aim of facilitating the standardization of care. To construct the triages, selected pre-established criteria from clinical findings in patients with Covid-19 were considered. The wide application of these triages will enable clinicians to make a better evaluation of treatment response at different stages of the disease and to make optimal use of the available health resources, although it may be necessary to recalibrate them as more knowledge is acquired. Furthermore, these triages may be useful tools for research purposes.

Calculation of the Triage Grade

The first step to calculate the triage grade was to identify the different criteria from the literature. Each criterion was then ranked between 1 and 5, depending on the clinical relevance and frequency of presentation. A top rating of 5 was awarded to each body systems (i.e., respiratory, cardiac, immune). Since several indices were used to evaluate some of the systems, values from each index were added to a maximum of 5. The final step was to assign weights in percentages to each criterion, then divided by 100 and multiplied by the corresponding grade. These weights, reached following the opinion of clinicians and researchers at institutions with experience in the field and after detailed consideration of the published literature, served as scaling factors to specify the relative importance of each criterion. The sum of all individual values for each criterion represented the overall triage grade. The following formula shows the calculation:

Triage grade = grade of criterion 1 x (%weight/100) + grade of criterion 2 x (%weight/100) + …. grade of criterion n x (%weight/100) = Total value

The total value of the grade defines the severity of the clinical status. Initially, it can be assumed that a total grade between 4 and 5 has the highest hazard, a grade between 3 and 3.9 has moderate hazard, and grades lower than 3 have the lowest hazard. This method was chosen because of its flexibility and ease of use, but it may allow recalibration, as required.

Triage of Covid-19 Infected People Outside Hospital ("Covid-19 Triage-1")

The objective of the Covid-19 Triage-1 was to assess the clinical status of patients with respiratory symptoms diagnosed or under suspicion of being infected by the SARS-CoV-2 that remain outside hospital. The triage would also allow the selection of the type of care required, including whether and when the transfer to a hospital may be required to receive specialized treatment.

To construct the Covid-19 Triage Score-1 the most frequently reported symptoms by Covid-19 infected people such as fever, cough, and shortness of breath, [5] were taken as the pre-selected criteria (Table 1). Less frequent symptoms like myalgia, headache, diarrhea, anosmia or ageusia were also taken into account collectively. Shortness of breath is the symptom reflecting a direct affectation of the lungs, and since these patients are more likely to have worse outcomes, it received the highest weight. Covid-19 seems to affect preferentially old age people, leading to worse outcomes, [5,6] therefore making a risk criterion. By contrast, children have experienced low infection rates by Covid-19 with little symptoms, and usually have good prognosis [7]. The pre-selected symptoms were assigned 50% of the total weight of Covid-19 Triage-1.

Incident	**Grade**					**Weight**
Symptoms	**1**	**2**	**3**	**4**	**5**	**%**
Age (years)	≤50	>50 up to 60	>60 up to 70	>70 up to 80	>80	**10**
Fever	>37°C to <38°C	>38°C up to 3d	>38°C up to 5d	>38°C up to 7d	>38°C up to 9d	**10**
Cough	negligible	minor	moderate	major	very intense	**5**
Shortness of breath	negligible	minor	moderate	major	very intense	**20**
Other symptons (myalgia, headache, diarrhea, etc.)	negligible	minor	moderate	major	very intense	**5**
Comorbid conditions						
Hypertension			treated with 1 medication	treated with 2 medications	treated with >2 medications	**5**
Diabetes			treated with 1 medication	treated with 2 medications	treated with ³2 medications plus insulin	**5**
Cardiovascular disease			CAD +/- CVD	CAD + CVD	previous MI +/- stroke +/- HF	**5**

Lung disease (COPD, asthma, idiopathic pulmonary fibrosis, cystic fibrosis)	<6mo	>6mo	>1y	>2y	>5y	**15**
Chronic kidney disease	<6mo	>6mo	>1y	>2y	>5y	**5**
Immunosuppression					yes	**5**
Malignancy			treated with radiotherapy or chemotherapy	treated with radiotherapy + chemotherapy	treated with radiotherapy + chemotherapy + immunotherapy	**5**
Body mass index (kg/m^2)		>25	>30	>35	>40	**5**

CAD, coronary artery disease; CVD, cerebrovascular disease; COPD, chronic obstructive pulmonary disease; HF, heart failure

Table 1: Covid-19 Triage-1.

The comorbid conditions associated with Covid-19, shown to represent a higher risk for complications and mortality, were assigned the other 50% of the weight to construct the Covid-19 Triage-1. [1,8,9] Hypertension, diabetes, cardiovascular diseases, chronic obstructive pulmonary disease, chronic kidney disease, immunosuppression treatments, and malignancy, have been shown to be associated to the worst outcomes, [1,8] and, therefore, were used as pre-established criteria. As explained above, and seen in Table 1, each criterion was given a unique weight to determine its level of influence on the overall score.

Since the presence of lung diseases and cardiovascular diseases are associated with worse outcomes in Covid-19, [1,8,9] they were given the highest weight. Other conditions such as chronic kidney disease, [10] malignancies and immunosuppressive treatments, [11] although less frequent, are also of particular risk for patients with Covid-19. Patients with ≥2 comorbidities may be at greater risk of poorer outcomes and, because of this, they should receive a greater surveillance.

Obesity is causally related to heart diseases, affects lung function and impairs the immune response. Besides, obesity influences the adaptive immune response to influenza virus, [12] and it has been linked to worse outcomes in Covid-19. [13-15] Because of this, the body mass index was also included in the Covid-19 Triage-1.

Triage of SARS-CoV-2 Infected People Inside Hospital ("Covid-19 Triage-2")

SARS-CoV-2 infected patients admitted to hospital have different degrees of clinical involvement and they may have a progression of disease severity needing a scaling of care. Because of this, a second triage, the Covid-19 Triage-2, was designed; for which, as seen in Table 2, a number of clinical and laboratory indicators for dysfunction of different body systems were taken into account.

Incident	**Grade**					**Weight**
	1	**2**	**3**	**4**	**5**	**%**
Respiratory abnormalities						**25**
PaO_2/FiO_2, mmHg (kPa)		<400 (55)	<300 (40)	<200 (26.7)	<100 (13.3)	
Respiratory rate (breaths per minute)	>20	>25	>30	>35	>40	
Chest x-ray and/or CT scan (% consolidation or GGO on each lung)*	<10	>10	>20	>30	>40 +/-pneumonia +/-pulmonary embolism	

Cardiac injury						**20**
Troponin I (hs-cTnI)>99th percentile upper reference limit					yes	
BNP >99th percentile upper reference limit					yes	
New ECG abnormalities					yes	
New ECO abnormalites					yes	
Immune/inflammatory response						**30**
C-reactive protein (mg/L)	£1	>1	>3	>6	>10	
Lymphocytes (normal range: 1000-4800 cells/μL)	<1000	<900	<800	<700	<600	
Cytopenia**			one lineage	two lineages	three lineages	
IL-6 (pg/mL)		<7	>7	>30	>100	
Ferritin (ng/mL)	>300	>1000	>2000	>4000	>6000	
Coagulation abnormalities D-dimer (ng/mL)			>250	>500	>1000	**10**
Serum albumin (g/dL)				£3,49	£2	**5**
Lactate dehydrogenase (normal range: 122-222U/L)	>222	>322	>422	>522	>622	**5**
Kidney dysfunction						**5**
Creatinine (μmol/l)	>84 in women >104 in men	>120	>140	>160	>180	
BUN (mmol/l)	>9	>11	>13	>15	>17	
eGFR (ml/min x 1.73 m^2)			<60	<45	<30	

BNP, brain natriuretic peptide; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; GGO, ground glass opacification; IL-6, interleukin 6; PaO_2/FiO_2, arterial oxygen partial pressure to fractional inspired oxygen ratio

*Chest x-ray scoring system from ref. 25

**Defined as hemoglobin <90g/L, platelets <100 x 10^9/L, and leukocytes <5 x 10^9/L or neutrophils <1.0 x 10^9/L

Table 2: Covid-19 Triage-2.

Covid-19 is primarily a respiratory infection; however, since the SARS-CoV-2 uses the Angiotensin-Converting Enzyme (ACE) 2 receptor for entry into target cells, a receptor that is predominantly expressed by epithelial cells of the lung, intestine, kidney, heart, and blood vessels, [16] it may cause a multiorgan affectation. The SARS-CoV-2 enters cells through endocytosis or membrane fusion by the ACE2 receptor [17] acting in concert with the host's TMPRSS2 membrane protease, that primes the spike S protein of the virus to facilitate the cell entry [18]. Preclinical studies with the SARS-CoV virus have shown a downregulation of ACE2 in the heart as a result of virus engagement with the ACE2 receptor [19]. This can be interpreted as part of the host defense mechanism in response to the infection to limit continued viral proliferation. However, the potential consequence of virus-induced ACE2 downregulation is the attenuation of the physiological role of ACE2, diminishing its anti-inflammatory effect and heightening angiotensin II effects including its pro-inflammatory, prothrombotic and pro-oxidant hazards.

Respiratory Involvement

Like other diseases associated with the coronavirus family, Covid-19 is a disease affecting mainly the respiratory system and progression to acute respiratory failure is the most severe outcome; a life-threatening complication that may require intensive respiratory support, endotracheal intubation and mechanical ventilation. Patients infected by SARS-CoV-2 and displaying respiratory failure typically exhibit diffuse alveolar damage with pulmonary edema, hyaline membrane formation, and interstitial mononuclear inflammatory infiltrate, [20] alterations that severely impair gas exchange. It is of critical importance to detect patients that may develop respiratory failure to enable the most appropriate clinical management, and even prevent its occurrence. In Acute Respiratory Distress Syndrome (ARDS), early intubation has been associated with survival improvement. [21] However, it is also important to note that up to 50% of patients admitted to the ICU do not require mechanical ventilation [22] and that the failure to apply optimal oxygenation and respiratory support may be harmful [23]. Therefore, to improve patients outcomes and make a better use of health resources, it would be advantageous to select patients that can be safely managed outside the ICU and of those that may benefit and require more advanced and invasive respiratory assistance.

The measurement of the ratio PaO_2/FiO_2 and the respiratory rate are suitable indexes to assess lung functional status and, therefore, they were considered for the Covid-19 Triage-2. Besides, the chest x-ray or CT scan, that can identify the lungs' damage caused by Covid-19, were also taken into account. In both cases, the typical changes consist in bilateral peripheral consolidations and/or ground glass opacities, [24,25] ranging from small to frank diffuse opacities depending on the stage of the disease [26].

Cardiac Injury

Patients with preexisting cardiovascular diseases have higher risk of contracting Covid-19 [5] and increased propensity to worse outcomes [27,28]. Individuals with Covid-19 can also develop new cardiovascular complications, such as heart failure, myocarditis, pericarditis, vasculitis, and cardiac arrhythmias with a marked increase in mortality. Between 8-28% of patients with Covid-19 show early evidence of cardiac injury or stress with elevated troponin plasma levels [29]. They also show elevation of Natriuretic Peptides (BNP), all of which are highly predictable of requirement for ICU admission, ventilation and death [30].

Viruses are cardiotropic and can induce cardiac injury. Thus, infections like the Respiratory Syncytial Virus (RSV) have been associated with a high rate of cardiovascular events [31]. However, it still remains unknown whether the cardiac damage caused by SARS-CoV-2 is due to a direct viral injury, stress alone or a combination of both, or even the consequence of the immunological response in the vascular system that, in turn, can elicit diffuse microangiopathy and thrombosis. Regardless of the primary cause, patients with evidence of myocardial injury should be monitored to receive appropriate cardiac treatment. Hence, the elevation of troponin I and BNP (both >99th percentile of the upper reference limit), and the appearance of new electrocardiographic and of echocardiographic abnormalities, that are associated with more severe disease and worse prognosis, [32,33] were incorporated to the Covid-19 Triage-2 (Table 2).

The Immune and Inflammatory Responses

The host inflammatory response against infection is characterised by the release of acute-phase proteins and pro-inflammatory cytokines as part of the innate and adaptive immune response. C-Reactive Protein (CRP) plays an important role in innate immunity as early defense mechanism against infections, its plasma levels reflect the severity of the acute phase reaction, and have been shown to be predictive of admission to the ICU and requirement of mechanical ventilation in viral infections [34,35]. Elevated CRP levels have also been shown in patients with Covid-19 and reported to be a predictor of disease severity and adverse outcomes, [36,37] and because of this they were included in the Covid-19 Triage-2.

Lymphopenia, with reduction in the circulating levels of CD4+ and CD8+ T cells, has also been a consistent finding occurring early in the course of the Covid-19 infection in over 80% of patients [38,39]. T-cell depletion has also been reported in different viral infections, some chronic infections, and cancer, an event that may diminish the host antiviral immunity [40]. The degree of lymphopenia is an important prognostic indicator in Covid-19 and, indeed, the recovery of lymphocyte count correlates with clinical improvement.

Furthermore, patients with Covid-19 can have elevated plasma levels of IL-1, IL-6 and interferon γ [41,42]. A subgroup of these patients may develop dysregulation of the immune response with a major immune inflammatory response and cytokine up-regulation, also known as the "Cytokine storm". These cytokines play an important role in a normal immune response, but are harmful if produced and released in large quantities. Therefore, to assess the severity of the inflammatory reaction, the elevation of IL-6 plasma levels was used in the Covid-19 Triage-2.

Ferritin, an intracellular iron storage protein, is another inflammatory plasma marker that has been shown to be elevated in plasma in a variety of infectious and non-infectious disorders, including Covid-19, [43] and as such it was incorporated to the Covid-19 Triage-2.

Coagulation Abnormalities

Due to excessive inflammation, hypoxemia, immobilization, and diffuse intravascular disease, a proportion of patients with Covid-19 develop coagulopathy and thrombotic complications which are associated with poor outcomes [44]. Of the various coagulation indices reported in patients with severe illness,

D-dimers are the most relevant from a prognostic standpoint, and values >1000 ng/mL have been associated with poor outcomes in Covid-19 patients [44].

Serum Albumin and Lactate Dehydrogenase (LDH)

Serum albumin has been reported to be an independent risk factor for mortality in patients with community-acquired infectious diseases, [45] and can also predict the severity of Covid-19, [46] and, because of this, it was included to the Covid-19 Triage-2.

LDH is a glycolitic enzyme in the cytosol and its elevated concentration in plasma is an indicator for cell damage. Elevation of LDH in plasma has been seen in patients with Covid-19 [47] and, although it has limited sensitivity and specificity, was also incorporated to the triage as a useful marker to monitor disease activity.

Kidney Dysfunction

Chronic kidney disease is a risk for poor outcomes in viral infections and has been reported in 4.3% of infected Covid-19 patients with severe clinical presentation [27]. In addition, acute kidney injury has been reported in 5.1% of patients with Covid-19 that is associated with a significant higher risk for in-hospital death [14]. Therefore, due to the impact of kidney disease in the outcomes of patients with Covid-19, the serum creatinine, blood urea nitrogen and the estimated glomerular filtration rate were used for the Covid-19 Triage-2.

Discussion

Here we have described two triages, Covid-19 Triage-1 and Covid-19 Triage-2, to be used in two different settings outside and inside hospital, respectively, to help with the assessment and surveillance of the clinical status and also with the treatment of patients with Covid-19. Patients with higher grades should be followed closely and, if necessary, be monitored for organ dysfunctions. Thus, it is expected that the early identification of clinical deterioration in patients inside and outside hospital will result in better clinical outcomes. In addition, the use of the triages may result in a better use of the available health resources.

The proposed triages are a simplified way of assessing the clinical status of Covid-19 infected people. They are quickly and easily obtained, so that they can be applied across large data sets, providing a practical and effective approach to expedite care, thus becoming a potent tool to improve clinical management. Because the clinical findings and the prevalence of comorbidities may differ among ethnic groups and countries, the use of the triages will facilitate the standardization and comparison of data among them, including the efficacy of different therapeutic interventions. An additional advantage of the suggested triages, as compared with other triages recently published, [48-51] is that each parameter receives a specific weight that can be adjusted depending on the importance of their presentation. In doing so, the clinical status can be evaluated quantitatively as opposed to the qualitative assessment proposed by other researchers.

Also the triages might provide clues on the pathogenesis of Covid-19 and be of critical importance for the design and performance of worldwide research studies. Indeed, the standardization of data may help to identify why some people are more susceptible than others to complications. At present, genetic studies are being carried out in young people to detect whether the presence of gene variants might alter the inflammatory response and the susceptibility to tissue damage seen in some cases [52,53]. Recently, it has been demonstrated a higher nasal epithelial gene expression of TMPRSS2 in black individuals [54] that may be an explanation for the higher incidence of infection and death rates for Covid-19 in this ethnic group [55].

In conclusion, the triages described here can be helpful tools in the management of patients with Covid-19, so that the associated morbidity and mortality can be reduced. The suggested triages permit a continuous rigorous evaluation by medics, scientists and public health officials so that the projections that can be made are robust and reliable. It is hoped that they would help to expedite care, facilitating the flow process and improving efficiency in the utilization of health resources, avoiding at the same time the potential discrimination and unequal application of triage criteria that may occur [2-4,56]. In addition, they may be useful tools for researchers to compare quantitatively in a standard way the clinical outcomes from different ethnic groups and geographical areas, and for the design of future studies.

Conflict of interest: Nothing to declare.

Authors' contributions:

Manuel Galiñanes: Conceived the idea and wrote the manuscript.

Esteban Reynaga: Helped with the selection of clinical parameters and biomarkers and also with the writing of the manuscript.

Márcio Borges Sá: Helped with the selection of clinical parameters and biomarkers and also with the writing of the manuscript.

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