Table 1
Cox proportional risks, univariate and multivariate analyses for hospital admission risk.

	Univariate			Multivariate		
	HR	95% CI	*P*	HR	95% CI	*P*
Age	1.05	1.04–1.07	< .0001	1.04	1.02–1.06	< .0001
Male sex	1.88	1.30–2.70	.0008	1.45	0.98–2.14	.06
HT	3.77	2.60–5.49	< .0001	1.37	0.88–2.11	.15
DM	3.83	2.61–5.62	< .0001	1.81	1.17–2.78	.007
Heart disease	4.06	2.63–6.27	< .0001	1.11	0.67–1.83	.68
Cancer	2.65	1.29–5.43	.008	1.09	0.51–2.32	.81
Dyslipidemia	3.35	2.32–4.85	< .0001	1.41	0.94–2.12	.09
Renal failure	3.43	1.40–8.39	.007	1.39	0.54–3.58	.48

HT: hypertension, DM: diabetes mellitus.

information bias. Despite including consecutive subjects, the gender distribution is not in line with the data published in the National Epidemiological Surveillance Network report available at the time of the analysis (52.2% women, 47.8% men),[5] and may reflect a selection bias (inclusion of a high percentage of health workers or caregivers). Our data also come from a health area that has experienced relatively low hospital pressure, so the admission criteria may differ from other areas or epidemiological situations with higher case saturation. This, or a different prevalence of comorbidities in other areas, would plausibly limit the generalization of our results. This study, then, is a preliminary description of a care model of patients with SARS-CoV-2 infection which could serve to guide other teams in the future design of patient follow-up programs or the implementation of referral criteria between care levels during the pandemic.

Conflict of interests

The authors declare that they have no conflict of interests related with the contents of this manuscript.

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Therapeutic limitation in elderly patients: Reflections regarding COVID19☆

Limitación terapéutica en pacientes ancianos: reflexiones a propósito del COVID-19

The SARS-CoV-2 pandemic has put the Spanish health system to the test, revealing an imbalance between clinical needs and the availability of resources (structures, equipment, and professionals) that has had serious consequences on the outcomes of patients, their families and health professionals themselves. This situation requires complex decision-making based on the classic principles of bioethics,[1] distributive justice, patient autonomy, beneficence and non-maleficience, to ensure the appropriate allocation of available resources in a scenario of shortfall. In our view, this distribution of resources must be based on maximizing benefits in the attempt to "save" the greatest number of patients who are more likely to survive.

The document published by the Spanish Society of Intensive Care[2] calls for performing triage on admission (a proposal we share) based on giving priority to patients with greater life expectancy (LE), an estimate that is unavoidably probabilistic and difficult to quantify. According to this document, patients older than 80 years of age with comorbidity will preferably receive non-invasive respiratory therapies (NIRTs), and those aged 70–80 years with no significant prior pathology would be candidates for invasive mechanical ventilation (IMV).[2]

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Table 1
Preliminary data from FRAGANCIA study.

	Total sample	Frail (n = 93)	Non-frail (n = 52)	p-Value	OR
Age (years)	79.2	82.2	77.5	0.680	
70–79 years	21.1%	22.6%	28.8%	0.402	
80–84 years	23%	20.5%	23.1%	0.709	
>85 years	35%	44.1%	19.2%	0.003	
Sex (%M and %F)	M55%/F45%	M51%/F49%	M53%/F47%	0.702	
Institutionalized	25%	39.8%	7.7%	0.0001	
IPC	60%	85%	27%	0.0001	
Barthel index				0.0001	
Severe BI	24%	37.6%	0		
Moderate BI	20%	31.2%	0	0.051	
Mild BI	37%	29%	50%	0.0001	
Independent	19%	2.15%	50%	0.0001	
Charlson index	5.8	6.77	5.39		
Frailty index	4.38	6.47	3.11		
Geriatric syndromes	56%	83.4%	19.2%		
Complications during admission	80%	86%	77%	0.121	2
Total days of admission	11.21	10.79*	20.19	0.002	
RICU	44%	34.4%	57.7%	0.007	
ICU	12%	6.5%	26.9%	0.001	
Death during admission	18.3%	30% (21 pats.)	19.2% (16 pats.)	0.123	1.826
<24 h	3%	3 pats.	2 pats.		
5 days	5.3%	7 pats.	4 pats.		
>5 days	10%	11 pats.	10 pats.		
Time until first admission	164 days	108 days	195 days	0.0001	
Death first year	28.4%	38.2% (26 pats.)	10% (4 pats.)	0.002	5.712

F: female; IB: Barthel index; ICU: intensive care unit; IPC: informal primary caregiver; M: male; pats.: patients; RICU: intermediate respiratory care unit.

When 2 patients are competing for the same resource, a clinician might decide to base their decision purely on age, as the highest mortality rate occurs in the older age groups (age group 70–79 years = 10.47%, and older than 80 years = 22.31%).[3] The older group includes individuals with more comorbidities and fragility; however, we should not make the mistake of considering them, *per se,* a group with less LE in whom NIRT or IMV would be pointless because of the scant benefit. In clinical practice, making decisions based on the 2 variables of age and comorbidity is not easy, due to the wide variety of comorbidities, many of which are not included in the most commonly used comorbidity indices, and their different impact on the patient's frailty if they are considered separately.

Joynt et al.[4] analyzed reasons for ruling out ICU admission and concluded that age, diagnosis, and disease severity were the main criteria for rejection. While it is true that the mortality of patients >80 years who are admitted to the ICU is high, at around 70% per year, these figures depend, fundamentally, on comorbidity[5] and frailty.[6–10] These data highlight the need for a more complex assessment based on the Frailty Index (FI) which, in addition to comorbidities, takes into account the patient's functional status and presence of geriatric syndromes.

In population-based studies, the prevalence of frailty varies between 4.9% and 27.3% and pre-frailty between 34.6% and 50.9%. Prevalence by age group is 7% in >65-year-olds and 20% in >80-year-olds[6] and between 23% and 30%[8,9] in ICU patients. In these cases, frailty was an age-independent prognostic factor associated with increased mortality during admission and the 6 months after discharge. The studies consulted recommend the use of tools to detect frail patients after admission to the hospital. The FI was the most widely used, as it has a good capacity to distinguish subgroups of patients, and its use could be extrapolated to the Covid-19 pandemic for the selection of frailer patients.

Our group is currently conducting a study that analyzes the impact of frailty on elderly patients admitted for respiratory failure who require non-invasive mechanical ventilation (NIMV): the FRAGRANCIA study (Study on the impact of frailty in older patients requiring NIMV). An intermediate analysis of the results, not yet published, suggests that frailty in the elderly population is associated with higher early mortality (<5 days from admission) and mortality at 1 year of follow-up (26 frail patients *vs.* 4 patients in the non-frail group, p = 0.002) (Table 1), and that the FI is able to differentiate these risk groups.

We are aware that the FI is not the only answer to the prioritization problems we have experienced during the Covid-19 pandemic, when resources were sometimes unavailable for even the youngest and healthiest of patients. In a recent editorial, published in *The New England Journal of Medicine*, the authors address the problem of having to choose between 2 or more patients for the assignment of resources, such as ICU admission.[11] The need to weigh up multiple ethical values in order to prescribe different interventions and allocate limited resources can generate different benchmarks for the weight assigned to each value in a particular case. This real situation that arose during the Covid-19 pandemic underlines the need to develop fair resource allocation procedures that include all the stakeholders involved in patient care, and the patient and family themselves, in order to develop prioritization criteria for decision-making in times of adversity, without transferring this burden to a single healthcare professional in a specific situation. At the present time, there are no valid criteria to deny ICU admission to people with good life expectancy. The lessons learned from this pandemic underline the need for the health system to increase its resources to adapt to emergency situations.

In adversity, respiratory medicine experts have demonstrated the value of our knowledge of NIRT in critical and semi-critical patients and the importance of the development of respiratory intensive care units (RICU). The RICU plays a role not only in the

treatment of the acute patient, but also in the weaning of ICU patients, and helps free up beds. The RICU has eliminated any argument for the need to reserve ICU beds "just in case". Refusing a patient access to the ICU in order to assign the place to another patient more likely to survive is justifiable in a pandemic,[11] but even more so when the initial patient can be transferred to a RICU, where IMV can be withdrawn and replaced by NIRT under a level of monitoring and care that is superior to a conventional hospital ward.

The development of joint care protocols with the collaboration of intensive care units, internal medicine, and emergency departments, together with respiratory medicine, is essential to maximize the management of available resources. Pre-selecting patients with easy, intuitive tools, such as the FI, is indispensable for improving decision-making.

Among the many changes that will emerge after the Covid-19 pandemic, we believe that one of the most relevant will surely be the expansion of RICUs and the leadership of respiratory medicine in decision-making on borderline patients, such as the elderly, unifying selection criteria, clarifying the concept of frailty, and integrating its use into our clinical practice.

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Hydroxychloroquine and Potential Drug Interactions in Older Adults

La hidroxicloroquina y las posibles interacciones farmacológicas en ancianos

Dear Editor,

Hydroxychloroquine has in vitro activity against severe acute respiratory syndrome coronavirus (SARS-CoV), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and other coronaviruses. It is currently under investigation in clinical trials for pre-exposure or post-exposure prophylaxis of SARS-CoV-2 infection, and treatment of patients with mild, moderate, and severe coronavirus disease 2019 (COVID-19).[1] There are no currently available data from Randomized Clinical Trials to inform clinical guidance on the use, dosing, interactions, or duration of hydroxychloroquine for prophylaxis or treatment of COVID-19 infection. Recently, Gautret and cols have reported that hydroxychloroquine treatment is significantly associated with viral load reduction/disappearance in COVID-19 patients and its effect is reinforced by azithromycin (drug interaction).[2] Preliminary results have confirmed that viral positivity in respiratory secretions was significantly decreased at day 6 in hydroxychloroquine treated COVID-19 patients versus those with supportive care, supporting the current choice of hydroxychloroquine as first-line treatment.[2,3] Despite of limited studies, nowadays, hydroxychloroquine is recommended for hospitalized patients confirmed COVID-19 patients, with mild-to moderate disease, age >65 years and/or underlying end organ dysfunction (lung, heart, liver, etc.), diabetes, coronaropathy, chronic obstructive pulmonary disease, arterial hypertension or severe disease.

General guiding principles are based on these considerations, however, the therapeutic window is quite narrow (cardiotoxicity/arrhythmia), requiring caution for use at higher cumulative dosages, taking also into account that therapy will be required mostly in older patients and/or in case of severe disease. In addition, the slow elimination and the variable pharmacokinetics of hydroxychloroquine frequently lead to delayed actions and a variable clinical response. It is possible that this variability arises partly from drug-drug interactions (DDIs) and genetic differences in the capacity to metabolize hydroxychloroquine, as has been shown for many other drugs.[4]

Contradictory results of the inhibitory effect of HCQ on cytochrome-P450 isoenzyme 2D6 (CYP2D6) activity in vivo have been published in humans. Generally, all drugs metabolized by CYP2D6 may inhibit each other's metabolism. Because of the great variety of drugs metabolized by CYP2D6 (antiarrhythmics, antihypertensives, β-adrenoceptor antagonists, monoamine oxidase inhibitors, morphine derivatives, antipsychotics and antidepressants), characterization of potential interacting drugs affecting the activity of this enzyme is clinically important and can improve the safety of drug treatment.[4] On the other hand, the P-