University of Louisville Journal of Respiratory Infections

MULTIMEDIA

International Respiratory Infections Society COVID Research Conversations: Podcast 3 with Dr. Antoni Torres

Julio A. Ramirez[1], MD, FACP; Antoni Torres, MD, PhD, FERS*

[1]Center of Excellence for Research in Infectious Diseases, Division of Infectious Diseases, University of Louisville, Louisville, KY; [2]Department of Pulmonology and Critical Care, University of Barcelona

*j.ramirez@louisville.edu

Recommended Citation: Ramirez JA, Torres A. International Respiratory Infections Society COVID Research Conversations: Podcast 3 with Dr. Antoni Torres. Univ Louisville J Respir Infect **2021**; 5(1): Article 11.

Outline of Discussion Topics

Section(s)	Topics
1–4	Introductions
5	“Spanish” influenza
6–9	Dr. Torres’ personal thoughts and experiences
10	COVID-19 hospitalizations in Barcelona
11	A threatening phone call
12–13	Origin of the CIBERESUCICOVID project
14	Baseline characteristics
15	Bloodwork at hospital admission; ICU admission vs. day 3
16	Treatments
17	Complications
18	Outcomes related to interventions
19	Viral RNA load in plasma associated with critical illness and dysregulated response
20	Follow-up with health care workers
21	Medical education
22	Conclusions
23–26	Interleukin 6
27–29	Ventilatory approach
30–33	Post-COVID syndrome
34–38	Impact on health care workers
39–41	Holidays and COVID-19 infection
42–43	New paradigm for medical education
44–45	Reducing travel for medical conferences
46–47	Improving treatment for COVID-19
48–53	Vaccination in Spain
54–57	Prioritizing clinical trials
58–65	COVID-19 as viral pneumonia
64–69	Thanks and sign-off

All figures kindly provided by Dr. Torres.

Edited Transcript

This conversation was recorded on February 9, 2021.

DR. RAMIREZ

(1) Thank you for coming today to this session of *COVID-19 Research Conversations*. Today I have the tremendous pleasure to have this conversation with Dr. Toni Torres. Toni, like other members of this conversation group, has been a friend of mine for many years, and I want to ask Dr. Torres to give us a brief introduction to himself. Toni?

DR. TORRES

(2) Thank you very much, Julio. I'm very glad to be here sharing this webinar with you; thank you for inviting me. My name is Antoni Torres; I am a Professor of Pulmonology and Critical Care at the University of Barcelona, and a researcher of respiratory infections for many years. So, it's my pleasure.

DR. RAMIREZ

(3) Thank you, and again, following the theme that we have in these conversations, first I will ask Toni to give us a little bit of an overview of what he considers to be the lessons learned in this presentation, "The Year of Living Dangerously," and after his presentation, we're going to discuss a little bit of what he's doing now. And then, we're going to move to the second part of the discussion, which will be how he sees COVID in 2021. Toni, do you want to start with your presentation?

DR. TORRES

(4) Thank you very much. Well, this is the title that I chose because I remember a film of this title featuring Mel Gibson. Well, I liked the film and I like the title because this is true: a very, very difficult year. I divided my content into my personal experience, what we did in research, and what we did in education. Personal experience: I have some personal thoughts, and I want to tell you the case of my brother-in-law and some fights in the hospital—it's very interesting, but we can discuss this later.

(5) Look at what happened in 1918 in Spain, during the so-called—or wrongly called—"Spanish" influenza. This[1] is from Burgos, a city in the middle of Spain, and these were the recommendations: the virus was "transmitted by small particles of saliva when talking or coughing," "avoid poorly ventilated places," "intense house cleaning," "follow medical advice and avoid ignorant recommendations such as smoking and drinking alcohol." And this was written in this official bulletin on October 4, 1918.

(6) Personal thoughts: this quote from Pasteur came to me that I learned many years ago, and it made an impression on me: "Microbes will have the last word." And I think this is true; I always thought that, and that's one of the reasons that I dedicated my life to investigating infections, respiratory infections in this case. Secondly, reflect that what happened in China was neglected. And why? I think we had the information in December, January, even February; we could have done a lot. We did intense preparations, for example, for SARS; I remember many, many meetings and many protocols, and SARS never came to Spain. And in this case, we did not do that. And then finally: Lombardia is very close. Why they did not lock down the frontiers until it was too late? We saw the cases in Lombardia; I cannot understand that.

(7) Let's take the case of my brother-in-law, which was very typical because health care providers had no experience with COVID at the time. Well, he was one of the first—he got COVID the third week of March. He's the director for an institution for mental discapacities, the Fundación Catalonia, and there was an outbreak there. He was diagnosed because he was in the foundation, not through public health; the public health system was failing. He had persistent fever at day 8 with cough. I recommended a chest X-ray first, which was normal, and then immediately, because I read the papers from China, I ordered a CT scan, according to Chinese literature, and the CT scan showed bilateral infiltrates. The conclusion of the radiologist was COVID in resolution. My brother-in-law called me and said, "I am okay because it's in resolution," and I said, "no, you have to go immediately to the hospital." And then, for that reason—among others—he was not admitted to the hospital, even with the CT scan; it was unbelievable. And finally a friend of mine, who is running a private institution here in Barcelona, admitted him, but he almost died.

(8) Continuing my personal thoughts—and this very sad—there were fights in the hospital. Infectologists and the people of the global health department seized power without consulting with pulmonologists, and pulmonologists only were called after two weeks and a lot of admissions, just as partners. Protocols were changed constantly based on poor and small observational studies; I was not managing those protocols. And they changed from hydroxychloroquine to hydroxychloroquine plus azithromycin plus remdisivir, etc., etc. I never have done that in my practice. I know that they had nothing to go on, but you have to be very careful. And then finally, the case of cor-

[1] See RTVE "Yes, the image about the 'Spanish flu' of 1918 that circulates on social networks is real" [in Spanish] (https://www.rtve.es/noticias/20200507/imagen-gripe-espanola-1918-archivo-burgos/2013540.shtml)

ticosteroids is very clear; corticosteroids were forbidden in the hospital because of the examples of SARS and metapneumovirus, even the guidelines of the Surviving Sepsis Campaign, and I think probably the the CDC or something—I don't remember—but corticosteroids were forbidden. But then clinicians started to use corticosteroids, and they observed that in some patients, corticosteroids were effective. And then, finally, the studies came, and this is one of standard treatments now; we cannot cure all of our patients, but corticosteroids work pretty well.

(9) Another problem: we ran out of protective equipment. That was terrible, and for that reason, many, many health personnel got infected. And then we had to buy this equipment from China, mainly through Spain, through the European Union—this is another problem to discuss, and it's very, very complicated.

(10) These are the hospitalized patients in Hospital Clínic Barcelona up to July—of course, now we have more—3543 patients and a total mortality of 8% overall (ward and ICU), and the mortality of patients in the ICU was around 30%; you will see that later on. And this is the evolution of the beds occupied in intermediate care units and in the ICU **Figure 1**; the crest on the left is the peak of the pandemic. And then we had a period of stability during the summer, but then in in September, it started again and is increasing. And now we are really in the third wave; 70% of the ICU beds in our hospital and in other hospitals are full of COVID patients. And this was due to inconsistent measures on some holidays that we had in December: the 8th and 9th because it's a national holiday, and then after Christmas. We can talk about Christmas later on; this is important.

(11) Research: what I did with research was to put all of my research group to work collecting COVID data, including data for ECMOCARD (probably you know of ECMOCARD—it's an international consortium; one of the leaders was previously my fellow—Gianluigi Li Bassi—and the senior leader is John Fraser), and they were collecting data from home. But I received a threatening call from one of my colleagues (I will not say their name, but this was the reality). He said, "you have to stop collecting data because you are not allowed to do that." Of course, I went first to the ethical committee and ECMOCARD, and in the next story, I will tell you about the IRB. And I was called to a committee in the hospital of the ICU directors of the several ICUs, and I had to explain everything that I was doing. Unbelievable. And this threatening call was from one of my colleagues in this department because I had the capability through the people in my group to collect many, many data.

(12) But fortunately, I received another call at night, at the end of March, from the director of a network in Spain, which is called Fever (might be you're aware of them, Julio). And he told me, "Toni, there will be an important call from the Central Government for Research, and I would like you to prepare a study to apply for a grant." And I thought that I should do that, because I wanted to do something for my patients, for my group, and for the society, and this was the opportunity. And then, at the beginning—this is important—some of my people in the research group lost control because they just wanted the glory. And what was the glory? The glory is to sign first one of the 90—I think there are 90,000 or more, 100,000 manuscripts now—and I said, "being cited is not what matters; this is very good, but nothing is going to change with that. I think it's better to do a good study." And then I applied as a PI for this institution, Instituto de Salud Carlos III. What I wanted to do is to study the risk factors, personalized prognosis, and 1-year follow-up in patients admitted to Spansih intensive care units with COVID-19 infection. This project is called CIBERESUCICOVID, and I got this grant for €1,750,000, which for Spain is probably one of the highest, and for my career as well; this was a lot of money.

(13) The project hypothesis at that time—this was the end of April—was that a significant percentage of hospitalized patients with COVID-19 are expected to require admission to the intensive care unit (20%), need mechanical ventilation (80%) and receive ECMO treatment (5%). And I think that these figures have proved to be true, at least in the first peak. And patients who survive the acute ICU episode will have a one-year cumulative incidence of death of 40%. And those who still survive will have functional respiratory sequelae, cardiovascular events, and poor quality of life at six months. I think that this has also proven true, although I don't know about the figure of 40%. It was a prospective/retrospective multicenter observational study of patients admitted to Spanish ICUs—only Spanish ICUs—and all patients eligible in each ICU are recruited when possible. So, we are recruiting all the patients. At that time, we said 50 Spanish ICUs; now we have 65. We said 5,000 patients for the clinical study; now, we have 6,000, as well as 1,000 patients for epigenetic/biomarker studies—we collected samples when possible in the first 24–48 hours, and the clinical data will be analyzed using artificial intelligence for the prognosis algorithms.

(14) This was the situation in November: more than 5000 patients included, 2,100 completed patients, and now these figures are 6,000 and 2,500. And now we have more than 65 centers with access to a REDCap system to include the data. Here is some of the information **Table 1**. Now, we are writing a paper with many more patients. And importantly, we collected this data sequentially, which is missing in most of publications; we have data on day 1, on day 3, the intermediate point, the day of extubation, the day of ICU discharge, the day

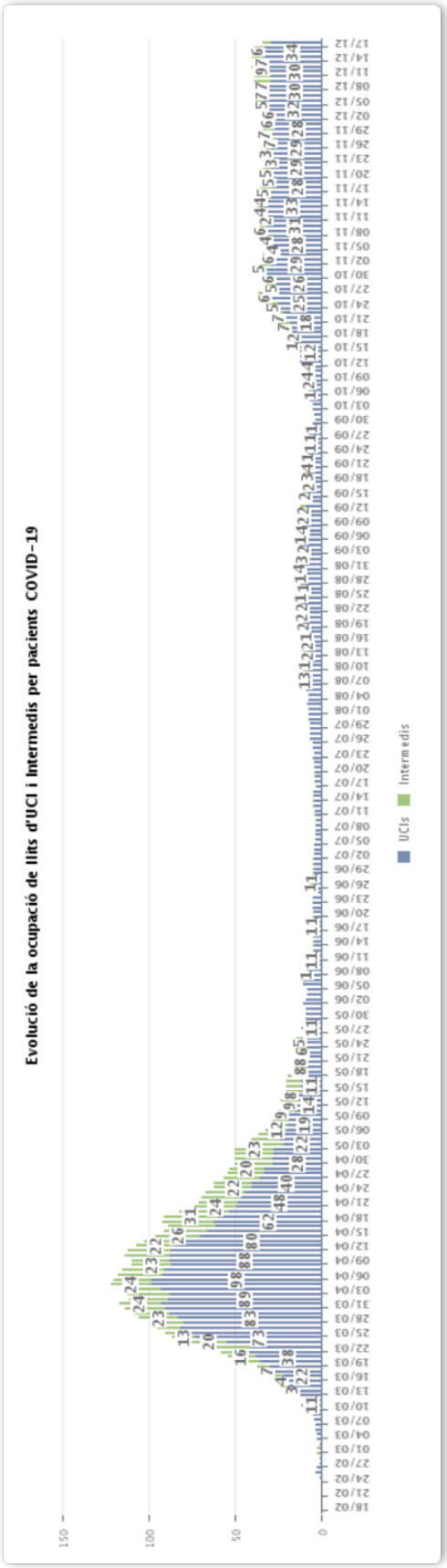

Figure 1. Evolution of the occupation of ICU and Intermedis beds by COVID-19 patients.

Table 1. Baseline characteristics.

	All (n=1318)	Alive (n=957)	Dead (n=361)
Sex, male	929 (70.49%)	663 (69.28%)	266 (73.68%)
Age, years	62.0 [53.0–70.0]	60.0 [50.0–67.0]	68.0 [62.0–75.0]
BMI, kg/m^2	28.65 [26.1–32.4]	28.65 [25.9–32.6]	28.69 [26.5–32.3]
Co-existing disorders, n (%)			
Hypertension	616 (46.7%)	382 (39.2%)	234 (64.8%)
Chronic heart disease	183 (13.8%)	103 (10.7%)	80 (22.6%)
Diabetes	307 (23.3%)	181 (18.9%)	126 (34.9%)
Chronic pulmonary disease	154 (12.0%)	75 (8.0%)	80 (22.2%)
Chronic kidney disease	90 (6.8%)	37 (3.9%)	53 (14.7%)
Previous 30 days admission, n (%)	35 (2.7%)	16 (1.7%)	19 (5.4%)

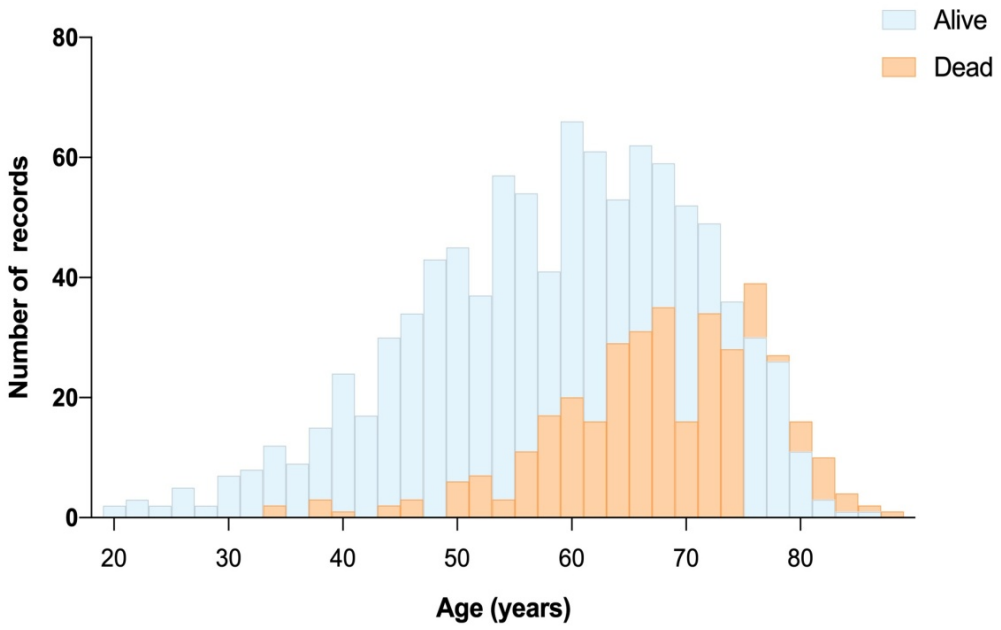

Figure 2. Age distrubtion of patients, dead and alive.

of hospital discharge, and the day of hospital admission. In this population, alive and dead, you can see the sex, and nothing is very different compared to what you have seen—and the comorbidities as well; you are very aware of that. And then you can see the distribution of age **Figure 2**; of course, the older people are dying more. And most of the patients were admitted to the ICU with bilateral infiltrates **Figure 3** and ARDS.

(15) There was not much difference between alive and dead patients when comparing leukocytes, lymphocytes, neutrophils, C-reactive protein, LDH, ferritin, and D-dimers at hospital admission. ICU admission versus day 3 is what I am looking at now, and the paper will will deal with this difference. What we found was that $PaCO_2$, lactate, and urea were all higher in dead patients than alive **Table 3**. When we looked at the mechanical ventilation parameters, the ventilatory ratio—a combination of the minute ventilation and the $PaCO_2$—was one of the significant variables **Table 4**. The compliance was as well—lower compliance in the patients who died at both day 1 and day 3. And you can see here no difference in peak pressure or driving pressure, but more prone positioning for those who died; this is because they were more sick.

(16) These are the treatments (**Figures 4 and 5**). You can see here a lot of treatments, especially in the beginning (hydroxychloroquine was withdrawn from the project). And you see what happened with corticosteroids: no difference comparing alive to dead in our population. And this is the hospital during the project and what happened to the patients **Figure 6**. As you know, median symptom onset was six days (dead) versus seven days (alive). I think that in some studies, the median time is shorter in patients with worse prognoses. For those who were alive, ICU discharge occurred at a median of 12 days, end of mechanical ventilation at a median 14 days, and hospital discharge at a median 26 days.

(17) The complications: mainly, you can see here **Table 5** that the complications are not very different, but acute renal dysfunction was higher in patients who died. This is something that has been observed before. Infectious complications: this is an interesting point—that in our study with this population, we could not find a significant difference in the percentage of patients alive or dead in terms of pulmonary, genitourinary, and bloodstream infections. There were a lot of patients with bacteremia in both arms, and *Pseudomonas*, *Enterococcus*, *Staphylococcus aureus*, MRSA and *Candida albicans* were the most frequent isolated microorganisms. And this is the the final data **Figure 7**, showing that 73% of patients were discharged alive—remember that all these patients went to the ICU. The total death rate was 27%.

(18) Outcomes in relation to interventions: you can see here that there were no differences between alive and dead patients regarding prone positioning **Figure 8** or tracheostomy **Figure 9**, but there was for renal replacement therapy **Figure 10**. There was no difference in ECMO **Figure 11**, but we didn't have a lot of patients at that time. Now, we have more and—this is interesting—this is data **Figure 12** that includes more patients regarding what happened on day 1, day 3 and day of extubation (extubation includes death), and you can see here that the patients who were alive had increased lymphocytes on day 3, the same for platelets, and no difference in in D-dimers. There was a difference in decreasing ferritin in patients that are alive. And—this is important, because there is a controversial issue—interleukin 6 in blood suffered a tremendous increase at day 3 compared to day 1 in the ICU, and most of the patients were mechanically ventilated on day 1, indicating that after mechanical ventilation, something goes wrong in some patients that dramatically increases interleukin 6. Finally, CRP is decreased in both dead and alive patients at day 3 after ICU admission.

(19) This is one paper that we published from our study, looking at SARS-CoV-2 RNAemia and the viral RNA load in plasma.[2] And you can see here **Figure 13**—and this is something that has been described as well—that viral RNA load in plasma is associated with critical illness and dysregulated response in COVID-19.

(20) Now some words about the follow- up of COVID. I am in charge of follow-up with health professionals that go astray. And really, it is very sad to see the long-term consequences that I observe in some of them. And I realized that I cannot do almost anything for them. And I thought, this is a very poor reward for them—this is something for the discussion section—because they risk their lives, and the reward was 1,500 viewers—in the last journal in the summary, depending on the category.

(21) Education: education was a real challenge. I am in charge of the respiratory diseases curriculum at the University of Barcelona, and I had to reorganize all the education for students in respiratory diseases. So, we have to record all the lectures; they could not do practical education; over the last year, we found a system of splitting students into small groups; we had many, many talks and webinars, and probably the consequence of this will be a shift in the paradigm of the presence of the professional in the lecture.

(22) Conclusions: of course, one year living in danger, and we still are in danger; we weren't prepared for this; it's been a great human and economical disaster, and the economic consequences will be disaster—*are* disaster—in Spain. And it is amazing that some politicians voted for death; they did not vote for life. And now in Spain, the elections for the Parliament of

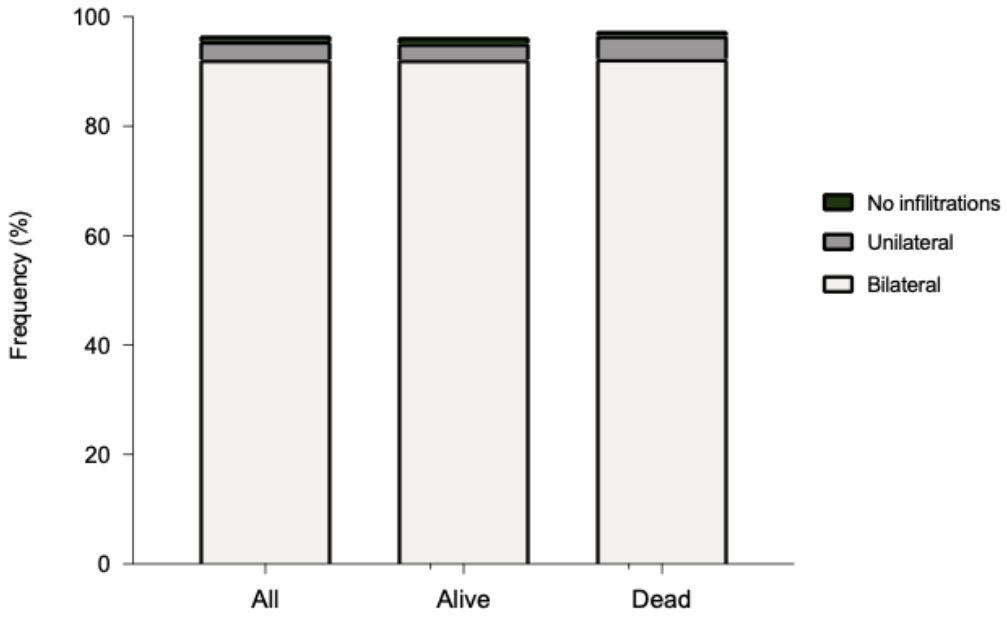

Figure 3. Frequency of lung infiltrates detectable via x-ray.

Table 2. Hospital admission.

	All (n=1318)	Alive (n=957)	Dead (n=361)
Leucocytes (10^9/L)	7.14 [5.23-9.86] (877)	7.0 [5.19-9.82] (643)	7.48 [5.5-10.07] (234)
Lymphocytes (10^9/L)	0.8 [0.55-1.06] (866)	0.8 [0.57-1.05] (637)	0.76 [0.5-1.1] (229)
Neutrophils (10^9/L)	5.8 [4.14-8.42] (583)	5.7 [4.16-8.4] (440)	5.95 [4.1-8.59] (143)
C-reactive protein	3.18 [1.38-14.16] (826)	2.99 [1.29-13.1] (606)	3.34 [1.6-16.25] (220)
LDH	410.0 [302.75-524.0] (544)	407.0 [304.0-519.0] (417)	443.0 [299.0-585.5] (127)
Ferritin	1077.0 [526.0-1944.0] (313)	1036.5 [531.25-1991.5] (248)	1131.0 [488.0-1619.0] (65)
D-Dimer	0.69 [0.4-1.22] (626)	0.68 [0.4-1.2] (473)	0.72 [0.43-1.28] (153)

Table 3. ICU admission vs. day 3.

	All (n=1318)		Alive (n=957)		Dead (n=361)	
	ICU ADM.	DAY 3	ICU ADM.	DAY 3	ICU ADM.	DAY 3
Mean arterial pressure (mmHg)	86.0 [70.0-99.0]	88.0 [74.0-100.0]	84.0 [70.0-100.0]	88.0 [74.0-100.0]	87.0 [65.3-97.3]	87.0 [73.0-99.0]
Heart rate (bpm)	80.0 [65.0-96.0]	79.0 [60.0-95.0]	80.0 [65.0-96.0]	78.0 [60.0-93.0]	85.0 [69.0-100.0]	82.5 [62.8-102.3]
Respiratory rate	24.5 [20.0-30.0]	23.0 [20.0-26.0]	25.0 [20.0-31.0]	22.5 [20.0-26.0]	24.0 [20.0-28.0]	23.0 [20.0-26.0]
FiO_2	70.0 [50.0-90.0]	50.0 [40.0-60.0]	70.0 [50.0-90.0]	50.0 [40.0-60.0]	77.5 [60.0-86.25]	55.0 [45.0-70.0]
pH	7.38 [7.31-7.43]	7.41 [7.35-7.45]	7.38 [7.32-7.43]	7.41 [7.37-7.45]	7.37 [7.28-7.41]	7.38 [7.31-7.43]
PaO_2 (mmHg)	89.5 [71.9-115.1]	82.1 [71.0-100.0]	90.0 [71.0-113.7]	82.0 [71.0-100.0]	87.4 [77.0-112.0]	83.0 [71.0-99.9]
$PaCO_2$ (mmHg)	42.0 [37.45-49.0]	44.5 [38.0-50.0]	41.0 [37.3-48.0]	43.0 [38.0-49.0]	46.0 [37.9-53.5]	46.9 [40.6-53.0]
Lactate (mg/L)	11.7 [9.9-16.2]	14.1 [10.0-18.2]	11.7 [9.9-15.2]	13.5 [9.9-18.0]	13.3 [9.4-20.7]	15.3 [11.0-19.8]
Creatinine (mg/L)	0.77 [0.62-0.96]	0.81 [0.64-1.14]	0.73 [0.6-0.9]	0.77 [0.62-1.01]	0.88 [0.71-1.31]	1.13 [0.79-1.86]
Urea (mg/L)	36.2 [24.0-51.0]	45.0 [31.0-68.0]	32.2 [22.0-48.0]	42.0 [28.7-61.0]	49.5 [30.0-64.1]	60.0 [40.0-87.7]

Table 4. ICU admission vs. day 3: ventilator parameters and pulmonary mechanics.

	All (n=1318)		Alive (n=957)		Dead (n=361)	
	ICU ADM.	DAY 3	ICU ADM.	DAY 3	ICU ADM.	DAY 3
Volume Control Mode, N(%)	262/1318 (19.88%)	602/1318 (45.68%)	185/957 (19.33%)	392/957 (40.96%)	77/361 (21.33%)	210/361 (58.17%)
Tidal volume (mL)	440.0 [400.0-480.0]	450.0 [400.0-480.0]	440.0 [400.0-480.0]	450.0 [400.0-480.0]	445.0 [390.0-492.5]	450.0 [400.0-487.5]
Ventilatory Ratio	1.66 [1.37-1.99]	1.83 [1.54-2.25]	1.56 [1.31-1.91]	1.75 [1.49-2.13]	1.78 [1.5-2.23]	2.06 [1.68-2.6]
Peep (cmH20)	13.0 [11.0-14.5]	12.0 [10.0-14.0]	13.0 [12.0-14.0]	12.0 [10.0-14.0]	13.0 [10.0-15.0]	12.0 [11.0-14.0]
Compliance (mL/cmH20)	35.58 [28.57-44.58]	36.67 [28.26-48.0]	35.58 [29.23-45.75]	37.5 [29.2-48.0]	35.16 [28.46-42.6]	34.55 [25.49-46.93]
Peak Pressure (cmH20)	31.95 [29.0-36.0]	30.0 [27.0-35.0]	31.5 [29.0-36.0]	30.0 [27.0-34.0]	31.95 [29.0-37.0]	30.0 [26.5-36.0]
Driving Pressure (cmH20)	12.0 [10.0-15.0]	12.0 [9.0-14.0]	12.0 [10.0-14.0]	11.0 [9.0-14.0]	13.0 [11.0-15.0]	12.0 [10.0-16.0]
Prone Position, N (%)	90/1318 (6.83%)	202/1318 (15.33%)	61/957 (6.37%)	113/957 (11.81%)	29/361 (8.03%)	89/361 (24.65%)

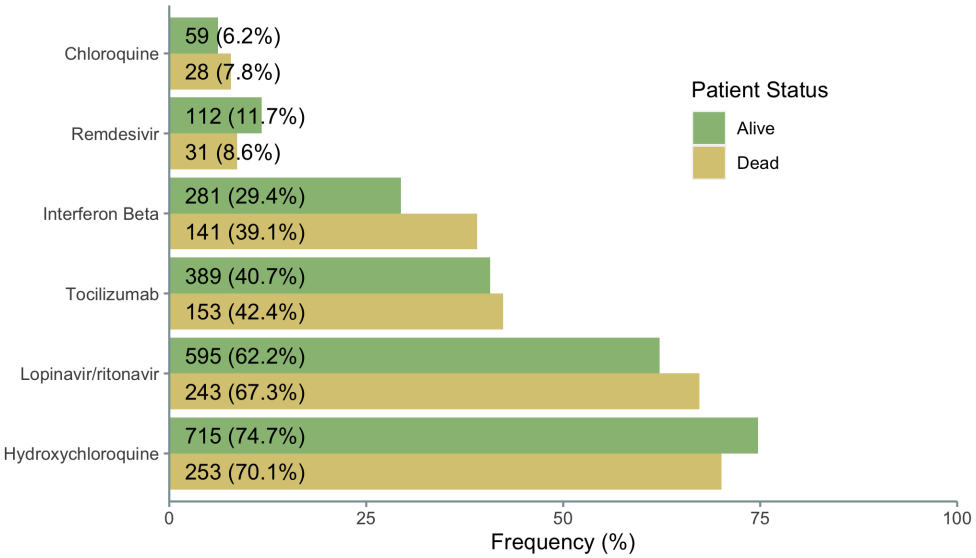

Figure 4. Anti-COVID-19 treatments.

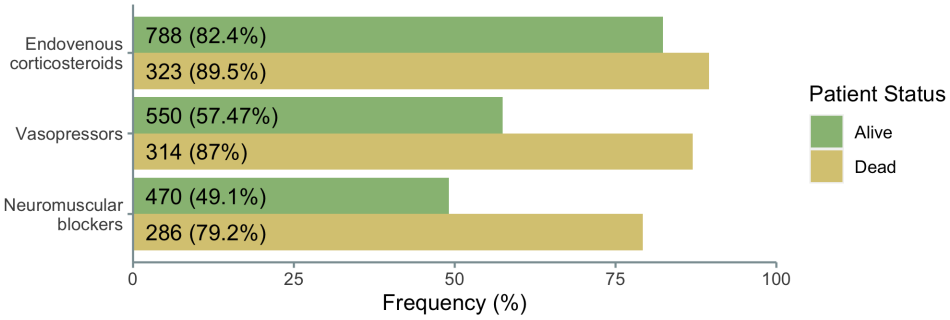

Figure 5. Adjuvant therapies.

Table 5. Complications.

	All (n=1318)	Alive (n=957)	Dead (n=361)
Pneumothorax	84/1318 (6.37%)	41/957 (4.28%)	43/361 (11.91%)
Pulmonary Embolism	135/1318 (10.24%)	107/957 (11.18%)	28/361 (7.76%)
Cardiac ischemia	61/1318 (4.63%)	33/957 (3.45%)	28/361 (7.76%)
Myocarditis	21/1318 (1.59%)	13/957 (1.36%)	8/361 (2.22%)
Heart attack	11/1318 (0.83%)	7/957 (0.73%)	4/361 (1.11%)
Acute renal dysfunction	407/1318 (30.88%)	215/957 (22.47%)	192/361 (53.19%)
Hepatic dysfunction	452/1318 (34.29%)	331/957 (34.59%)	121/361 (33.52%)

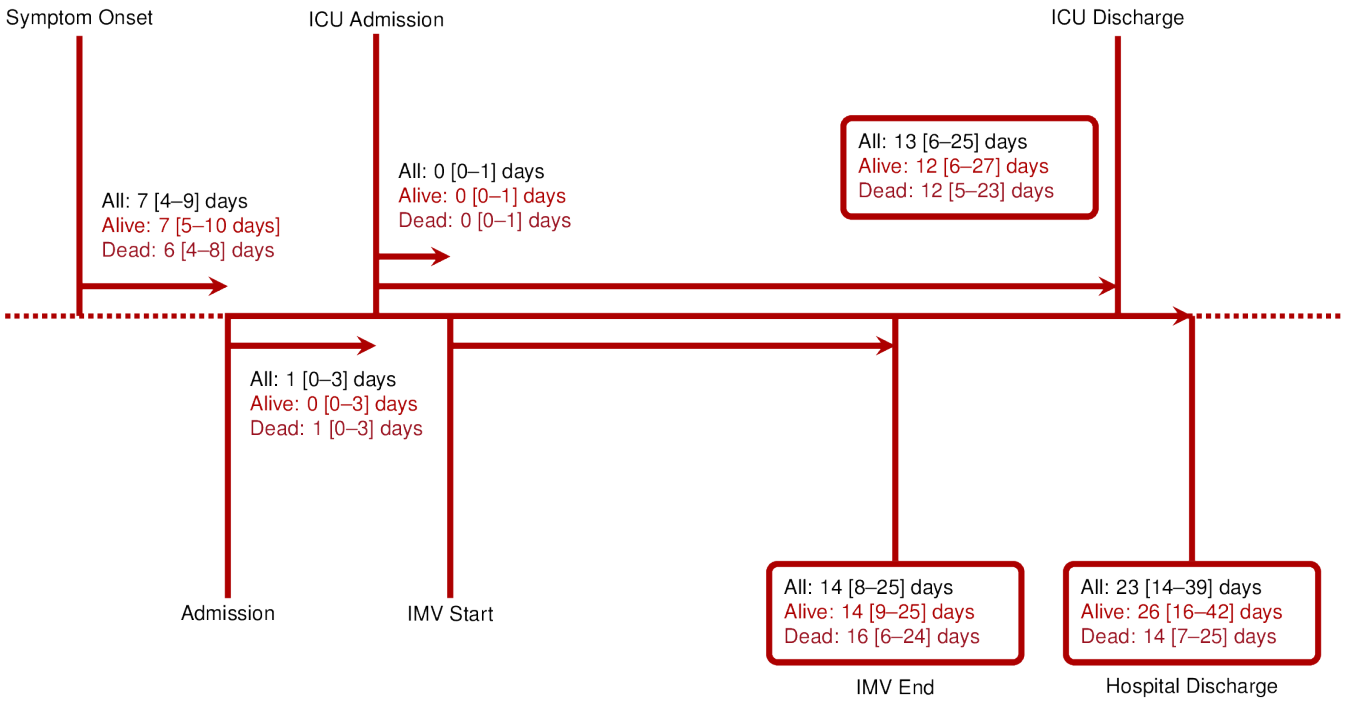

Figure 6. Supportive treatments.

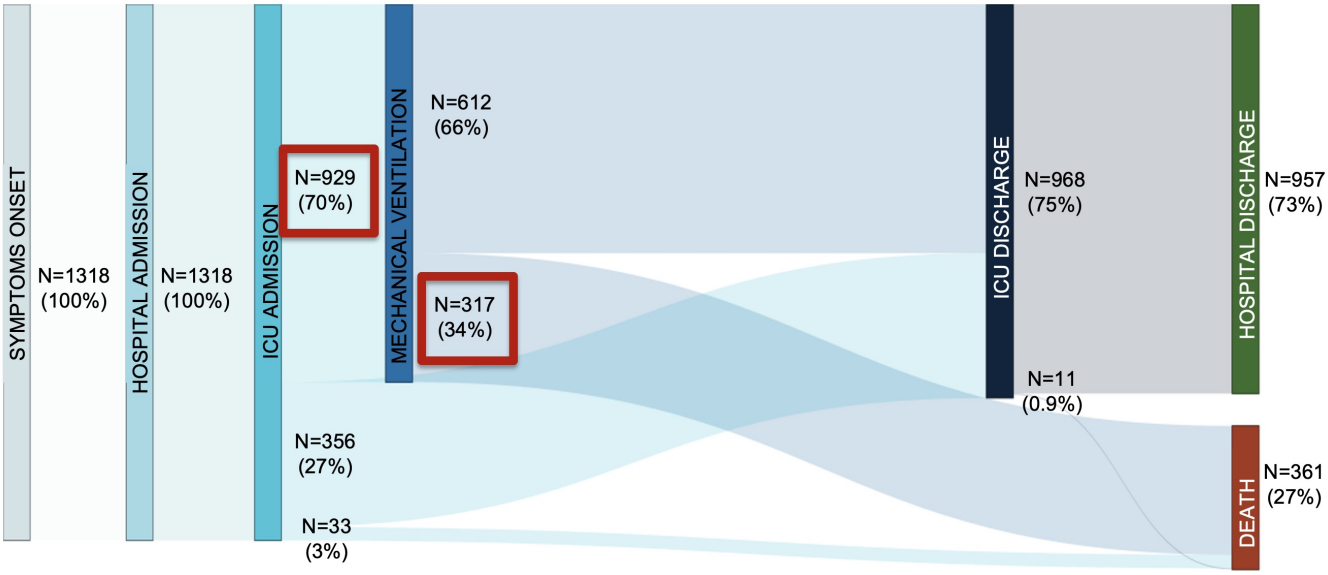

Figure 7. Main outcomes—patient journey.

Table 6. Infectious complications.

	All (n=1318)	Alive (n=957)	Dead (n=361)
Infectious focus			
Pulmonary	469 (35.6%)	328 (34.3%)	141 (39.1%)
Genitourinary	210 (15.9%)	161 (16.82%)	49 (13.6%)
Bloodstream	277 (21.0%)	177 (18.5%)	100 (27.7%)
Skin and soft tissue	54 (4.1%)	39 (4.1%)	15 (4.2%)
Gastrointestinal	17 (1.3%)	13 (1.36%)	4 (1.1%)
Osteoarticular and bone	1 (0.08%)	1 (0.1%)	0 (0%)
Infectious agent			
Pseudomonas aeruginosa	181 (13.7%)	125 (13.1%)	56 (15.5%)
Enterococcus	139 (10.5%)	104 (10.9%)	35 (9.7%)
Staphylococcus spp (no S. aureus)	111 (8.4%)	77 (8.1%)	34 (9.4%)
Candida albicans	90 (6.8%)	50 (5.2%)	40 (11.1%)
Staphylococcus aureus	79 (6.0 %)	55 (5.8%)	24 (6.7%)

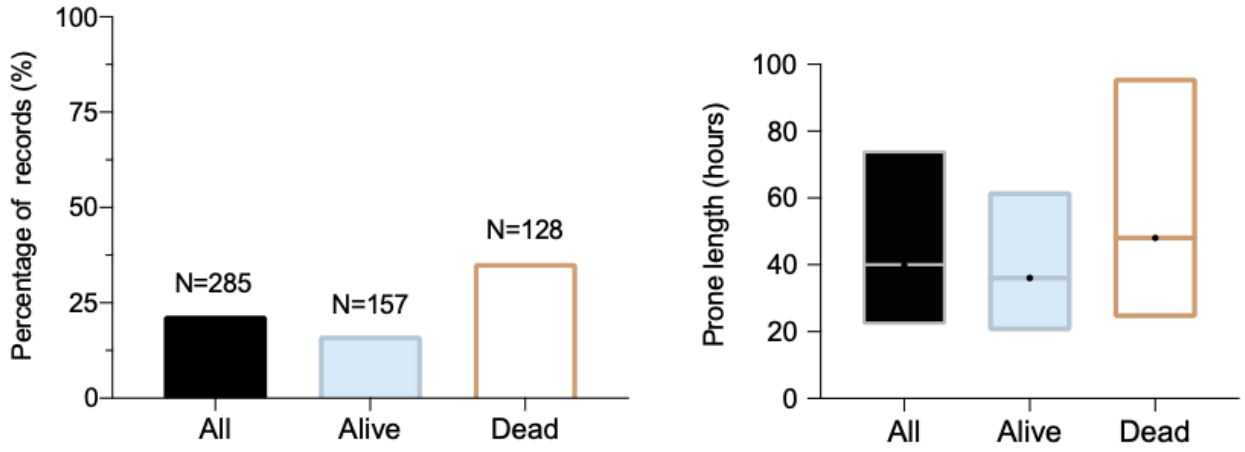

Figure 8. Outcomes in relation to prone positioning.

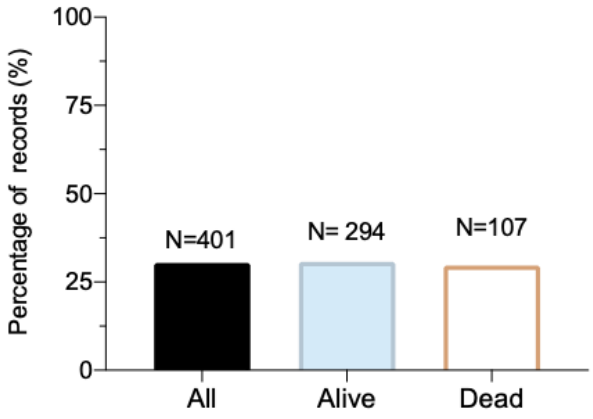

Figure 9. Outcomes in relation to tracheostomy.

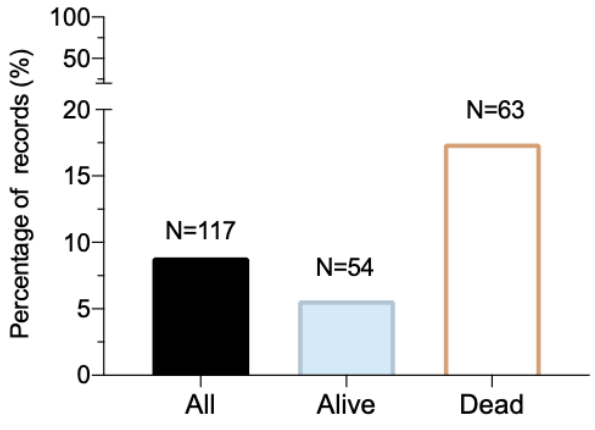

Figure 10. Outcomes in relation to renal replacement therapy.

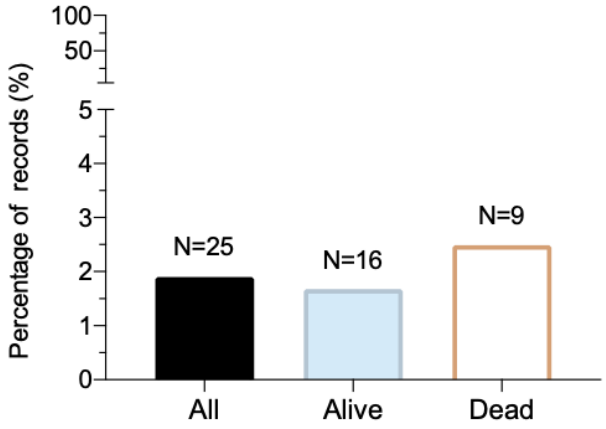

Figure 11. Outcomes in relation to ECMO.

Catalonia will be February 14, and the Catalonian government decided to postpone these elections—imagine: the elections of a country of 8 million persons, but the Spanish government refused the change of elections. And now we'll have elections for politicians' interest—other people that voted for death. But on the other hand, it was an opportunity for research and education and an opportunity to know solidarity and non-solidarity. Thank you for very much for this opportunity, it was really very nice to be with you. God bless you.

DR. RAMIREZ

(23) This is so interesting that this is a quote unquote "respiratory infection," but your presentation is a comprehensive experience of essentially all your life as an investigator and so much social impact of this disease at every level. So many questions I would like to ask you, but I want to ask you only one or two questions from the science of your research, and then I would like to move to the second part. Very impressive—the data on on interleukin six, where you see this separation of the high levels of interleukin 6 in patients that die and low levels in patients that are alive. And this also brings up the tocilizumab studies and all the ways that we tried to block interleukin 6, and it seems to be that blocking interleukin 6 didn't give us the effect we were looking for. What do you think is its role? What is interleukin 6 doing?

DR. TORRES

(24) I think—well, the role or the cause of this increase?

DR. RAMIREZ

(25) Yes, well, both: is interleukin 6 the chicken or the egg? What do you make of this in the pathophysiology of this disease?

DR. TORRES

(26) Well, I think despite the controversies about the cytokine storm, initially, interleukin 6 overall is not so high compared to ARDS, or sepsis of community-acquired pneumonia, for example; with sepsis, this is clear. But something happens in the middle; after 48 hours of mechanical ventilation, something happens—I don't know the reason—and whatever it is, it's very bad, because then the host cannot control this inflammation, and inflammation is bad for the lungs and for all the organs. And I want to look at whether this is a cause of wrong mechanical ventilation. This is one of my hypotheses, but I'm not sure of it. I have the data; I have to see if these patients have a different tidal volume—have a non-protected ventilation, for example. This could be one of the reasons; otherwise I don't understand because these patients are treated equally. I have to look at the treatments as well. I have to look at several things, but something is wrong between days 1 and 3 that we do or that is genetically marked, perhaps. I don't know.

DR. RAMIREZ

(27) But it's important that you've been thinking about this, and I can see your thought process. Do you think that somehow—the quote unquote "respiratory failure" of COVID and the pathophysiology at the alveolar capillary level—do you think that this virus is doing something different, that they will require a different type of ventilatory approach?

DR. TORRES

(28) Probably not; the utilitarian approach is protec-

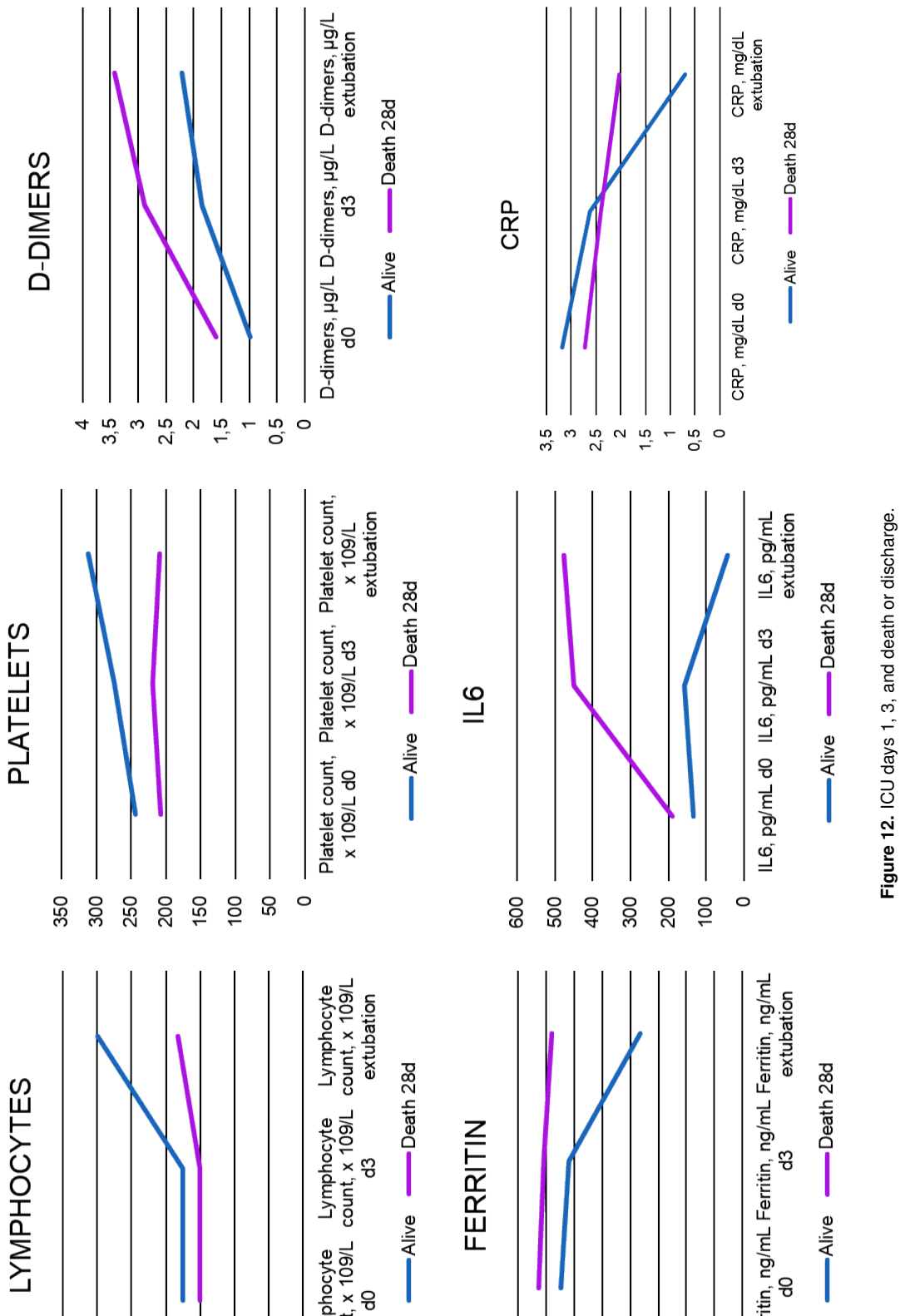

Figure 12. ICU days 1, 3, and death or discharge.

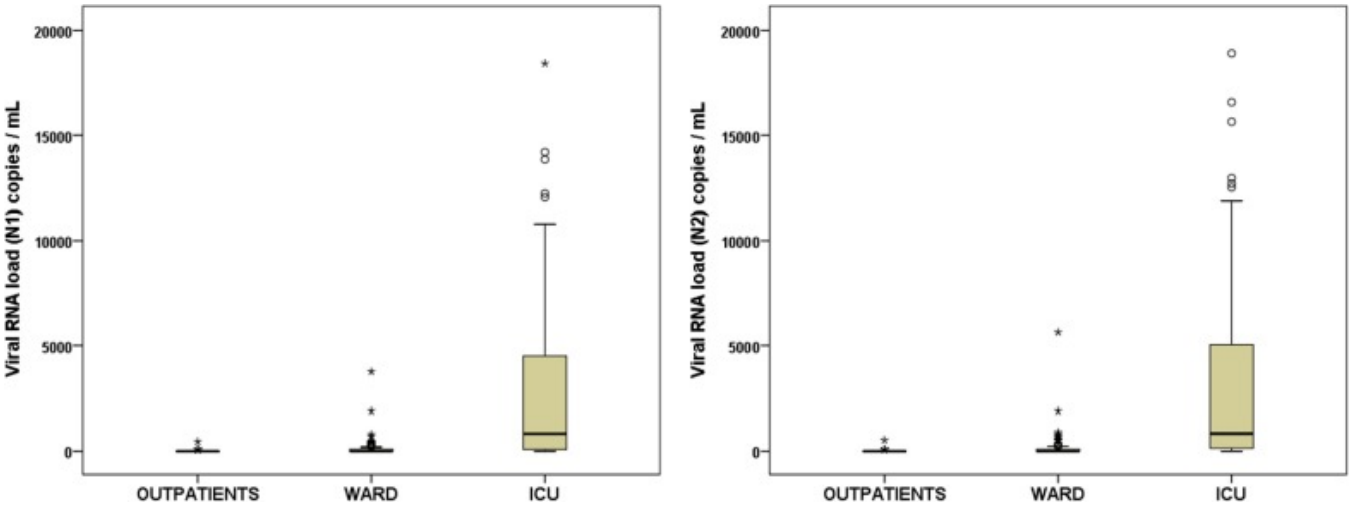

Figure 13. Viral RNA load in plasma, targeting the N1 region (left) and the N2 region (right), in the three groups of patients. Results are provided as copies of cDNA per mL of plasma.

tive ventilation for everybody, but this is not so different because what is protective ventilation? This includes a low tidal volume less than 6 cc/kg and a plateau pressure of 30. So, again, we have to look at the deltas, because with the deltas we will know, but not all the patients are similar. These patients are elderly; they have comorbid conditions—COPD for example—and then not everybody has the same vasal compliance in the lung.

(29) And then, maybe we are doing a harmful ventilation in some of them because the compliance is different; the compliance of a young person is not the same as that of the elderly—the vasal compliance—and maybe what we call "protective" ventilation is not so protective. This is what we learned from ARDS, but that was for non-COVID ARDS, and it might be different, or maybe there is something that is genetically already programmed. This is something we're looking into, but again, to understand what happens, we need to know the difference between day 1 and day 3 or day 4. This is part of the point of my study because at day 3 of mechanical ventilation in a patient with ARDS, you still can do something; you can modify something; you can, for example, lower the tidal volume, try to decrease the plateau pressure, or even protective extracorporeal membrane treatment stimulation. Why not?

DR. RAMIREZ

(30) Very good; very interesting. Congratulations on the grant, by the way. Another question: what are you seeing in your post-COVID follow-up clinic in health care workers? Because there's so much—in every city all over the world now, we have developed these post-COVID clinics as we see the consequences.

DR. TORRES

(31) Well, when I see these patients or phone them, those who are persistently sick complain of fatigue, a general tremendous fatigue, very similar to what I have seen in patients whom I have diagnosed with chronic fatigue syndrome in the past. They do something apparently very simple, and then they have to rest. Others have cardiac alterations, arrhythmias that are difficult to manage. And importantly, they complain of a strange pain in the thorax; this is also very common. And since I have seen a couple of patients with very clear pericarditis, I suspect the virus affects the pericardium and the pleura. Do you remember the concept of dry pleuritis, the viral pleuritis?

DR. RAMIREZ

(32) Yes.

DR. TORRES

(33) Okay, I think this is a viral pleuritis or pericarditis, with this difficult to understand pain that sometimes is in relation to the moment, sometimes not. But I don't think that this is dangerous; this is going to disappear with time, similar to the Bornholm disease.

DR. RAMIREZ

(34) Very interesting. Moving now into the second part of this conversation, which is how do we see COVID-19 in 2021. We discussed health care workers with post–COVID-19 syndrome. What is your feeling about health care workers in Spain experiencing this because there's this persistent pressure with more COVID cases in the hospital; here in Kentucky, one of

our lead infectious disease specialists died of COVID. Then, we have the full spectrum: everybody knows a health care worker who died; in every hospital, we have health care workers who died and some with chronic problems. And everybody knows health care workers who decided to have an early retirement.

DR. TORRES

(35) Yes.

DR. RAMIREZ

(36) Then how do you see the impact? And you alluded a couple of times to the role of the government; how do you see the impact in health care moving forward for ICU staff or for anybody in the hospital?

DR. TORRES

(37) Yes, well, first, what I see now in the health care personnel is irritability and depression. I have seen some cases of deep depression because this intensity is impossible to sustain; it's impossible for the brain to accept it. And then some of them are very tired and very irritable, and they cannot sleep well. It's also very difficult now to find nurses in Spain. The reason is that before the pandemic, the Spanish nurses went to the United Kingdom and to Germany because they are paid better there, and here it was very difficult for them to have a fixed position. And so if this is going to be maintained, this current situation—which is, I suspect, the case, and we can discuss that later on—it's going to be a terrible problem for Spain at least, for sure. The advantage now is that we are better prepared; we have more experience. And now, the third wave is going to be just as bad as the first wave—this is what the data indicate—but the number of infections is decreasing. So if this is going to last for some years, it's going to be very difficult.

(38) The politicians and educators will have to change things, perhaps give a rapid formation—rather than years long—for nurses. A lot of our nurses are from South America, so there is immigration from South America to Spain, and from Spain to the north of Europe. And this is the case with many, many physicians. And then, when our residents realize that they will be better paid elsewhere, they leave. I think that politicians should use the funds that the European Union plans to give us—they told us next June; I don't understand that. Why next June? Why not now? We need the money now, not next June. And they will have to invest in health, in ICU beds, in personnel, and in equipment. And the society is in favor of that. But I have seen many bad things from the society as well.

DR. RAMIREZ

(39) You mentioned what happened at Christmas and other holidays, particularly with young people; the patients that you see in the ICU are primarily elderly, but the people in the society who complain that they can't go out for tapas and so on are primarily the young people. How do you see this moving forward?

DR. TORRES

(40) Well, the mean age is lower now in the ICU; we are seeing people around 40 years old getting very sick. But of course, the higher percentage is the elderly population. And these people probably get COVID from young people enabling the transmission of the disease. They don't understand; what I have seen in society is that they think that they will never get COVID, and if they ever do get it, it's not going to be dangerous for them. And for that reason, what they want is to socialize, despite all they are seeing. We have had about 55,000 deaths in Spain since the beginning, in a country of 36 million. This is a lot, but they don't care. I remember that a couple of weeks ago, I went out for dinner (sitting outside and everything), and the people there were not wearing masks. So, I told them, "please use the masks." And they were very angry with me, and I just had to leave.

(41) And then Christmas. Christmas was a problem because it is so ingrained in the brain of the Spanish people—the holidays, not the religion, the holidays. Christmas means shopping, means stop working, means vacation. That's the young people; they wanted to do all that. On the other hand, it is very difficult to explain to the elderly—for example, my mother is 93, and my mother-in-law is 92—it was very difficult for them to understand that we were not going to celebrate anything this year. And a lot of people who celebrated got infected or died. And now we are seeing the consequence of of that. This was Christmas.

DR. RAMIREZ

(42) This is the society. Now, going back to another topic that you mentioned: the change in education. Everybody agrees that probably, this online form of education is here to stay, but at some point, you mentioned that the professional will no longer be in the classroom? You're in charge of education at the University of Barcelona; what will medical education look like moving forward?

DR. TORRES

(43) I think that we will keep the lectures online, but we will do seminars with the professional present to solve doubts, for example. I think this is going to be much more efficient, probably, because if you record the lecture, you use the same slides that you would use in the class. And if the students do not ask questions during the lecture, then I think that we can save time—

even using that time to prepare the lectures better—and then meet the students in seminars or small groups to resolve doubts or to do in-depth review of other aspects.

DR. RAMIREZ

(44) Yes, some of these changes are here to stay.

DR. TORRES

(45) I think so. Importantly, we we are not going to travel anymore for lectures, probably. And this is good because remember: the last time I met you was in Saudi Arabia, I think, or in Dubai; do you remember? Traveling to the other side of the world to give a lecture that you can do online, and then you can answer all the questions perfectly, is a waste of time. For us, this is a release.

DR. RAMIREZ

(46) No question. And then going back to COVID, you mentioned that it will likely continue for a couple of years, while a lot of people have been saying that they were looking at this year as the end of COVID. But with all the variants that we have from South Africa, Brazil, and England, you could argue that this may continue for some time. You mentioned that steroids is one method of treatment, but it's not too impressive. What do you think a more effective treatment will be: an antiviral, blocking the immune response, improving ventilation?

DR. TORRES

(47) Steroids are useful for some of our patients, and we see a lot of patients that improve rapidly. I think that we need to know more about phenotypes—in which phentoypes steroids are effective or not. This is important; we don't know the answers. But steroids work in most of the population, and you have seen that there is a difference between alive and dead patients in our population in relation to corticosteroids. Second, antivirals: we need new antivirals. I don't know if you saw the news yesterday; there is a Spanish investigator at Mount Sinai, who has come out with a new antiviral 100 times more potent than remdesivir that clears COVID completely in mice.[2] We need something like that in the first period of the disease. And then, in the period of inflammation, of course, we need to use specific anti-inflammatory drugs to block the inflammatory response without being harmful for the patient. If tocilizumab is effective, nevertheless, what we're seeing with tocilizumab is many more infections. So we need antivirals from the very beginning—new antivirals.

DR. RAMIREZ

(48) And then, before I let you go, I need to ask you what happened in Spain with the vaccines.

DR. TORRES

(49) Well, at the very beginning, without the input of pharmaceutical companies, I applauded them, but I think that I was probably wrong; the interest of the industry and money is always beneath the surface. Pharmaceutical companies have done a lot of good because they provide a lot of input for trials, which is very helpful, but now what is happening with vaccines? We aren't getting the vaccines now because AstraZeneca says that they have changed the deal with the European Union, and Pfizer has reduced production—what is happening? Does this mean that these industries are in association with other countries? The European Union is very angry with AstraZeneca. We need to know what is behind this.

DR. RAMIREZ

(50) Yes, yes, well, transparency has not been really—

DR. TORRES

(51) No, although a lot of people from the industry are very honest, of course.

DR. RAMIREZ

(52) I will say that regarding some of these transactions at every level—

DR. TORRES

(53) Well, these are very high level transactions. I just received one dose of the vaccine, and I have to receive the second next Tuesday, but then they were saying on the radio this morning that it is not certain that we have vaccines for the second dosage.

DR. RAMIREZ

(54) Now, another question: every week a new trial is announced, all the way through vaccine studies to antiviral studies to immunomodulatory studies. How do you decide what trials to do at your institution? I was talking to Mike Niederman the other day, and they have put together a committee to decide who is doing what trial.[3] I found this interesting because, at least in my experience, we've always had the industry contact one investigator, and the investigator decides yes or no.

[2]Plitidepsin, developed by Adolfo García-Sastre et al. at Mount Sinai University, New York.[3]

[3]See Ramirez JA, Niederman MS, Schenck EJ. International Respiratory Infections Society COVID Research Conversations: Podcast 2 with Dr. Michael S. Niederman and Dr. Edward J. Schenck. Univ Louisville J Respir Infect **2021**; 5(1): Article 6.

DR. TORRES

(55) For us, this is a still individual; the industry contacts the investigator. If you decide to go ahead, there is a committee in the hospital who have to be informed, but you are free to send the protocol to the IRB. Especially at the beginning, it was very individual; now it is better organized, and there is a committee that decides whether the hospital is going to participate or not.

DR. RAMIREZ

(56) This is a new way to look at all this because, again, traditionally the industry selected one investigator, and they decided, but of course, now we have to develop more and more committees to organize all the research activities because we are going to keep doing research on COVID for a long time.

DR. TORRES

(57) I agree with having committees to decide because even these committees are experts; they can decide on the most interesting trials or what will potentially be more effective for the patients at the end because there are some trials that are going to fail or will be very difficult to understand.

DR. RAMIREZ

(58) Going into clinical trials—we've never used corticosteroids for pneumonia before COVID-19.

DR. TORRES

(59) No, never. I think this is a new invention.

DR. RAMIREZ

(60) And there's a lot of discussion with people who are doing trials in pneumonia—these new outcomes point this way or that—

DR. TORRES

(61) Well, pneumonia was managed by pulmonologists, and by intensivists when the pneumonia was severe, but not by infectologists. You are the exception—you funded CAP research, and there is a school of CAP study—but the others are pulmonologists, in Europe as well and in Spain. Now, infectologists and epidemiologists are making decisions, and they don't typically know about pneumonia. And that's what this is; this is a viral pneumonia.

DR. RAMIREZ

(62) Yes, that's plain and simple; it's a viral pneumonia.

DR. TORRES

(63) But then, we have to use our experience with pneumonia and what we learned.

DR. RAMIREZ

(64) In our hospital—I don't know what your experience has been—a significant percentage of the patients do not have pneumonia; we consider them COVID patients because they have a positive PCR, but the reason for admission was something that is not related to COVID. But then they are enrolled in COVID studies. Should it be the case that to be in a COVID study, you have to have pneumonia?

DR. TORRES

(65) I think so, yes—admitted for pneumonia. The trials should not include patients with another disease solely because they have a positive COVID PCR because this is going to bias the results. The problem is that they are using this classification for trials, and if you look at the scores of 30-day mortality, still PSI in COVID is one of the best, very similar to others that combined several things together. You can't just use PCR; you have to use PSI. It's a viral pneumonia.

DR. RAMIREZ

(66) Okay, well, we've been talking for one hour. As always, it has been a pleasure to have you and to hear your experiences. Probably, we will do this again at some point as your research evolves.

DR. TORRES

(67) Keep very safe and healthy.

DR. RAMIREZ

(68) Okay, we'll keep in contact. And I want to thank everybody that is listening to these conversations. And I will always mention that if someone has any specific question for you, Toni—

DR. TORRES

(69) Send me an email, yes—no problem.

DR. RAMIREZ

(70) Okay, very good. Thank you very much. Be safe. Thank you.

DR. TORRES

(71) Goodbye.

Received: March 29, 2021

Accepted: April 2, 2021

Published: April 2, 2021

Funding Source: The author(s) received no specific funding for this study.

Conflict of Interest: All authors declared no conflict of interest in relation to the main objective of this work.

References

1. Yes, the image about the 'Spanish flu' of 1918 that circulates on social networks is real [in Spanish]. RTVE **2020**. Available at: https://www.rtve.es/noticias/20200507/imagen-gripe-espanola-1918-archivo-burgos/2013540.shtml. Accessed 14 February 2021.

2. Bermejo-Martin JF, González-Rivera M, Almansa R, et al. Viral RNA load in plasma is associated with critical illness and a dysregulated host response in COVID-19. Crit Care **2020**; 24(1): 691. doi: 10.1186/s13054-020-03398-0. PMID: 33317616.

3. White KM, Rosales R, Yildiz S, et al. Plitidepsin has potent preclinical efficacy against SARS-CoV-2 by targeting the host protein eEF1A. Science **2021**; 371(6532): 926–31. doi: 10.1126/science.abf4058. PMID: 33495306.