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International Respiratory Infections Society COVID Research Conversations: Podcast 1 with Dr. Francesco Blasi

Julio A. Ramirez[1], MD, FACP; Francesco Blasi[2], MD, PhD*

[1]Center of Excellence for Research in Infections Diseases, Division of Infectious Diseases, University of Louisville, Louisville, KY; [2]Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy

*j.ramirez@louisville.edu

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Edited Transcript

This conversation was recorded on January 14, 2021

DR. RAMIREZ

(1) Today, I have the pleasure to have with me my friend, Dr. Francesco Blasi, who will tell us about the lessons that he learned concerning COVID in his city: Milan, Italy. Then we will discuss, if there is time, a little of how he sees COVID in 2021. To start, Francesco, will you give us a brief overview of your position now in Milan, and then can you start with your lessons learned?

DR. BLASI

(2) Yes, thank you very much, Julio, is a pleasure to to be here sharing with you the lessons we learned in COVID-19. You know that Italy was the epicenter in Europe; the disease started there, and then it spread everywhere. I'm a professor of respiratory medicine and part of the Department of Pathophysiology and Transplantation at the University of Milan. In my hospital, which is the main university hospital in Milan, I'm head of the Internal Medicine Department and run the Cardio-Respiratory Unit and Cystic Fibrosis at the center here in Lombardy, the area around Milan. I work mainly on respiratory infection, as I said, and my interest moved from COPD to lung transplantation and cystic fibrosis.

(3) The target of today is to give you some idea of what happened in Italy, particularly in the area of Milan, during the last year. One of our key tasks was to create stability in a time of instability, which is on-going. In dealing with this, I think evidence-based practice is key, and we have seen how important clinical expertise is when dealing with a new disease. On the other hand, it is also important to consider what the patient wants. Combining these factors, you will probably develop the best practice for dealing with the disease.

(4) I think that the Coronavirus gives us a rocket stimulus for health care management in our area. One of the main problems in the management of COVID-19 was and is how to deal with infection in the community. Clearly, the virus has been a strong stimulus for technological innovation, considering, for example, how fast the preparation of new vaccines has been. In eight months, around five new vaccines have been developed for the disease. The other point is to determine the best care to be applied to our patients in terms of therapy.

(5) During the first two weeks of March last year, we had a mortality of about 40% in my unit, and then we started to change our therapeutic approach to include steroids, anti-inflammatory drugs, and anti-coagulation drugs, and the mortality rate dropped down to 18%. I think it is important to evolve our medical care for COVID—understanding the needs of our patient, understanding what we're doing and trying to standardize our approach. We must improve and evolve our approach, both our therapeutic approach and also, in general terms, our management approach.

(6) Just to start, this is the first paper published by our intensivists from Milan, looking into the first 1600 patients admitted to the ICU in Lombardy (**Table 4—Appendix**).[1] It was immediately understood that the mortality and severity of the disease is related to the number and kind of comorbidities that the patient has, as well as to their age. These are the two main points that appear to be underlined by this paper, and I'll show you how this was confirmed by the other paper we published.

(7) One of the main problems was that we started with about 800 beds in the ICU in Lombardy, and by April, we had more than 4,000 beds, but still this was not enough to treat every patient that needed invasive ventilation. So we tried to select as best we could which patients should be in the ICU to give the best opportunity to our patients. Of course, it was very hard to choose which patients should be intubated and which should not.

(8) We changed our approach and management, starting from the emergency room. We divided our emergency room into 2 separate sections: one for patients with suspected COVID, the other for patients with no suspicion (**Figure 1**). We moved each patient through one of the three columns—the green pathway, yellow/red pathway, and triage for non-COVID patients. We divided the emergency room with dedicated radiologists, one for suspected COVID and one for patients with no suspected COVID. Then we went through the pathway to possible discharge or moving the patient to a general ward, high dependency unit, or ICU. This was very important starting from the very early time in COVID.

(9) The critical aspect of this was the education of our personnel because we were not used to PPE (**Table 1**). We began with lectures and live demonstrations, then in-situ simulation, and then random calls to try to understand if the personnel were ready for these new approaches to the patient. And this involved not only the ICU, but all the health care workers in our hospital. We had over 3,800 personnel who took training, and we endeavored to give them all the information that we possibly could.

(10) Psychological support was also critical. It was important in the first wave, but even more so in the second

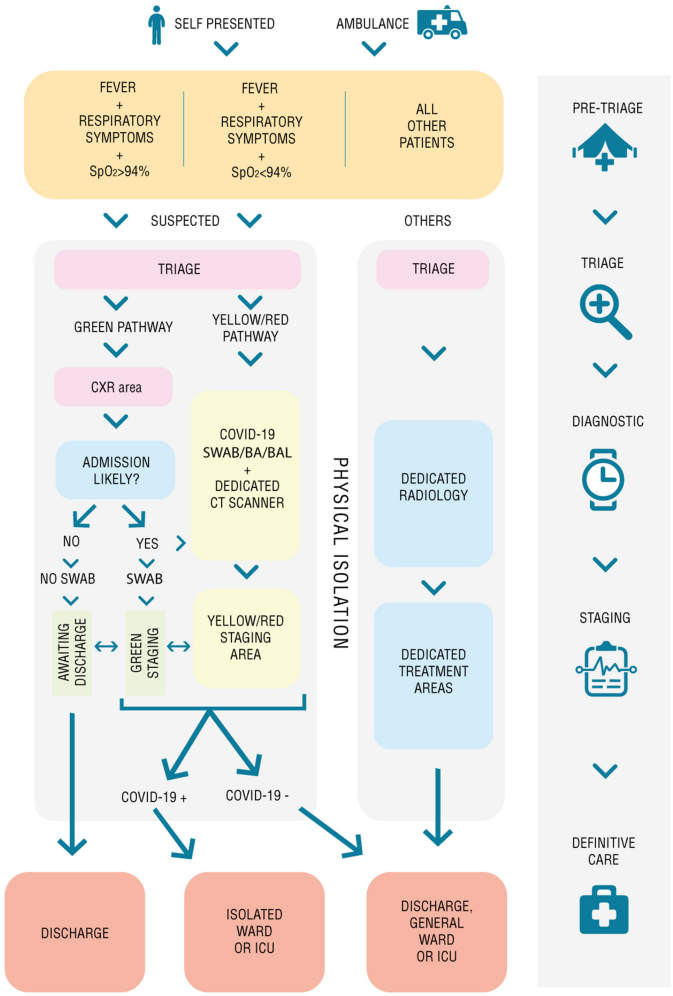


Figure 1. Patient flow within the hospitals from presentation through assessment to final disposition. Green (minor), yellow (moderate) and red (immediate) triage codes based on local emergency department triage protocol. *CXR*, chest X-ray; *BA*, bronchial aspirate; *BAL*, bronchoalveolar lavage; *CT*, computed tomography; *ICU*, intensive care unit.[2]

Table 1. COVID-19 healthcare workers training scheme.[2]

Training sessions	Activities	Duration	Participant numbers	Involved personnel
Lectures with live demonstrations	PPE donning and doffing	1 h, 3 times a day	Small groups <25 persons	ICU medical staff, ICU nurses, healthcare assistants
	PPE explanation			
In-situ simulation	PPE donning	1 h	1–2 doctors	
	Airway management of suspected or confirmed COVID-19 patients	All day rotations	2–3 nurses	
	Isolated patient handling (low-resource prone positioning)			
	Doffing of PPE			
Random calls	Surprise assessment with PPE checklists	20 min	1 person at a time	

wave because in the first wave, COVID-19 was novel, and health care workers were heroes for working to save lives, but in the second wave, patients, relatives, and health personnel had a fatigue of COVID-19.

(11) We also needed to manage respiratory failure and the increased oxygen requirement (an almost 5-fold increase) in the hospital, which required technical adjustment of the plants. Use of helmet CPAP increased from 9–10 a day to more than 140 a day.

(12) In my own unit, we decided to have a multidisciplinary team, involving the high dependency unit, pulmonologists and cardiologists (**Table 5—Appendix**). We established a cardio-respiratory unit with 44 beds, where patients would be ventilated but also followed by a cardiologist directly. The idea was to provide a very specific way to work for each of our physicians and nurses, and each physician was involved in the initial evaluation of the patient, choice of respiratory support, identification of signs of sepsis or multi-organ failure, etc.

(13) We have fellows helping each physician: respiratory specialists, cardiologists, nurses, and physiotherapists—we have 10 physiotherapists working with us, which was very important for the evaluation of respiratory ventilator oxygen support and for early mobilization of the patient. The cardiologists had an important role in determining appropriate therapy for hypertension and management of cardiac complications that are highly significant in COVID. And then we have consultants specializing in infectious disease, rheumatology, and intensive care. The intensivist visits twice a day—morning and evening—to evaluate the patient and discuss the opportunity for intubation or non-intubation.

(14) We decided to standardize the use of different respiratory support measures (high-flow oxygen, CPAP, NIV, or intubation) according to two parameters: PaO_2/FiO_2 ratio and respiratory rate (**Table 2**). We also standardized the therapeutic approach as soon as possible, starting from antipyretic drugs to treatment of systemic hypertension using different antihyperintensive drugs (**Table 6—Appendix**).

(15) For many patients, there was no possibility of oral nutrition, so we had to use feeding tubes or enteral feeding. Sedation is an important consideration, particularly for patients coming from the ICU; we have delirium in many patients after a long period of intubation. Life support is also very important; we try to prevent the patient from suffering from respiratory failure and hypertension, particularly for patients treated with anticoagulation.

(16) Looking into the data, the number of comorbidities correlates with mortality; the same is true for age—being older than 65 years is significant in terms of mortality (**Figure 2**). And we look to the successes and failures of CPAP treatment in COVID-19. I report here (**Table 3**) some of the parameters that are important, particularly the role of inflammation: CPAP failure is more frequent when you have a high level of inflammation, high level of risk of thromboembolism, and the level of FiO_2 is also important—if you need a very high level of FiO_2, the risk of CPAP failure is higher.

(17) Another factor is the prone positioning of a patient treated with CPAP. A prospective cohort study from our group of intensivists was published in the *Lancet*, which observes a positive effect of prone positioning and contemplates the possibility of long-term prone positioning.[6] We also examined prone and lateral positioning in a paper published in *Chest*.[7] For some patients, it works, and for others, it doesn't work. What happens in the first hour is significant in understanding whether prone or lateral positioning is working. This will require more study, but it is clearly important in understanding the possible role of prone and lateral positioning for patients in CPAP.

(18) We have patients with different compliance and different shunt fraction (**Figure 3**), which led us to consider the possibility that patients have different responses and different kinds of acute respiratory distress syndrome in COVID, which led to a highly controversial paper.[8] Gattinoni and his group of intensivists in Milan looked into the two possible phenotypes: type L and type H. Type L is a patient with COVID pneumonia with low elastance, low ventilation-to-perfusion ratio, low lung weight and low lung recruitability. For these patients, the suggestion is to treat with an increase of FiO_2 and non-invasive support. Type H patients have high elastance, high right-to-left shunt, high lung weight, and high lung recruitability. For these patients, the recommendation is to treat the condition as severe ARDS, with higher PEEP, prone position, and extracorporeal support. This paper was really controversial, but it is interesting because it led to a huge discussion about the physiology of ARDS in COVID.

(19) We published a paper last year using CHA(2)DS(2)-VASc scores for risk of thromboembolism in the lungs, and the higher the score, the higher the risk of mortality and intubation.[9] The resultant curve (**Figure 4**) is not so good, but it's not so bad. Certainly this score may be useful to identify patients at risk. Looking again at the risks factors (**Figure 5**), age and comorbidities, especially hypertension, seem to be significant for mortality.

(20) The cardio-respiratory unit is important because COVID implies the involvement of both the heart and the lungs. This is a paper published from another group in Milan and in Bergamo, looking at the hemodynamic profile of COVID-19.[11] They found

Table 2. Proposed respiratory support based on the severity of acute respiratory failure.[3]

Acute Respiratory failure	Alternative
P/F ratio $>$ 300 and respiratory rate (RR) $<$ 30	Low-flow nasal cannula oxygen or Venturi Mask or Reservoir Mask set with the aim of target SpO_2 92–96%
	HFNC 40 L/min and FiO_2 set with the aim of target SpO_2 92–96%
P/F ratio 100–300 and RR $<$ 30	Helmet CPAP with PEEP 5 or 7.5 cmH2O and FiO_2 set with the aim of target SpO_2 92–96%
P/F ratio $<$ 100 and RR $<$ 30	Helmet CPAP with PEEP 5 or 7.5 cmH2O and FiO_2 set with the aim of target SpO_2 92–96%
P/F ratio $<$ 100 and RR $\geq$ 30 and/or respiratory distress	NIV (Also to consider in case of: CPAP failure, hyper-capnia). NIV starting parameters: PEEP 12–16 cmH20 PS set with the aim of Vt 4–6 ml/kg and FiO_2 set with the aim of target SpO_2 90–95%

Abbreviations: *P/F ratio* arterial pO_2 divided by the fraction (percent) of inspired oxygen, *HFNC* High-flow nasal cannula, *CPAP* Continuous positive airway pressure, *FiO_2* fraction (percent) of inspired oxygen, *NIV* Non-invasive ventilation, *PEEP* Positive end-expiratory pressure.

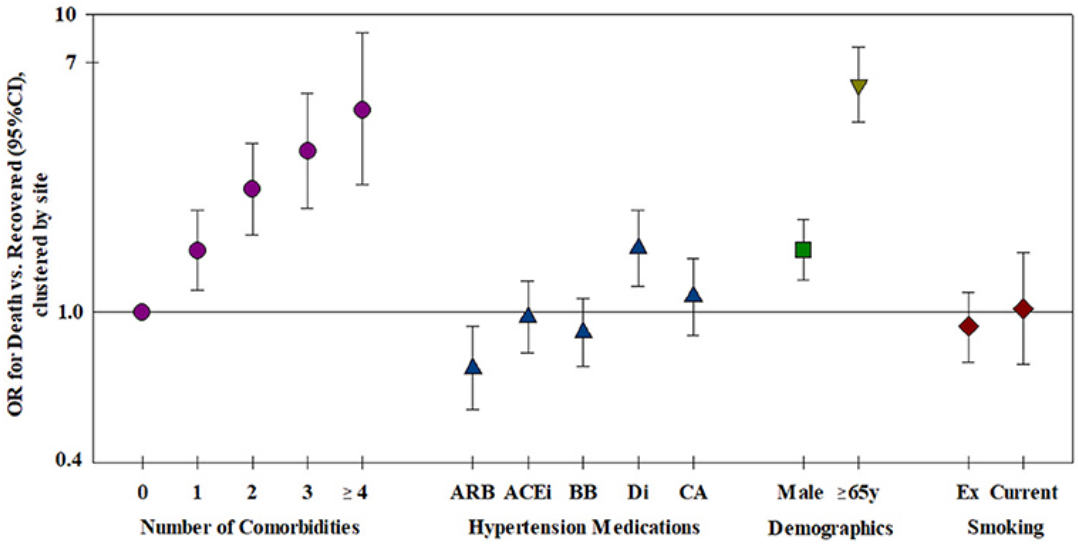


Figure 2. Risk factors for mortality—all risk factors were included in the model, clustered by site (n = 2,868). *ARB*, Angiotensin receptor blocker; *ACEi*, Angiotensin converting enzyme inhibitor; *BB*, Beta-blocker; *Di*, Diuretic; *CA*, Ca-antagonist.[4]

Table 3. [Excerpt] Baseline characteristics, continuous positive airway pressure (CPAP) treatment and outcomes of the study population according to CPAP failure or success.[5]

	CPAP success	CPAP failure	p-value
CPAP initiation and treatment			
FIO2 % (n=154)	50 (50–60)	60 (50–70)	<0.0001
PEEP cmH2O (n=154)	10.4±2.2	11.4±2.4	0.01
Increase of PaO2:FIO2 ratio of at least 20% from oxygen therapy to CPAP	53 (64.6)	33 (48.5)	0.047
Increase of PaO2:FIO2 ratio of at least 30% from oxygen therapy to CPAP	51 (62.2)	27 (39.7)	0.006
Days of CPAP treatment (n=153)	8 (5–14)	4 (3–7)	<0.0001
CPAP complications			
Pneumothorax	0 (0.0)	1 (1.4)	0.45
Pneumomediastinum	0 (0.0)	2 (2.9)	0.20
Haemodynamic instability	0 (0.0)	9 (12.9)	0.001
Intolerance	10 (11.5)	11 (15.7)	0.44
Ulcer	2 (2.3)	0 (0.0)	0.50
Study outcomes			
Weaning from CPAP to oxygen therapy	84 (96.6)	6 (8.6)	<0.0001
Days from CPAP initiation to weaning to oxygen therapy (n=87)	7 (4–12)	7 (1–8)	0.31
Intubation	0 (0.0)	34 (48.6)	<0.0001
Days from CPAP initiation to intubation (n=34)		3 (2–5)	
Mortality in HDU	0 (0.0)	36 (51.4)	<0.0001
Days from CPAP initiation to HDU mortality (n=36)		5 (3–10)	
Length of hospitalisation (n=138)	18 (14–25.5)	8 (4–22)	<0.0001
In-hospital mortality	0 (0.0)	45 (64.3)	<0.0001

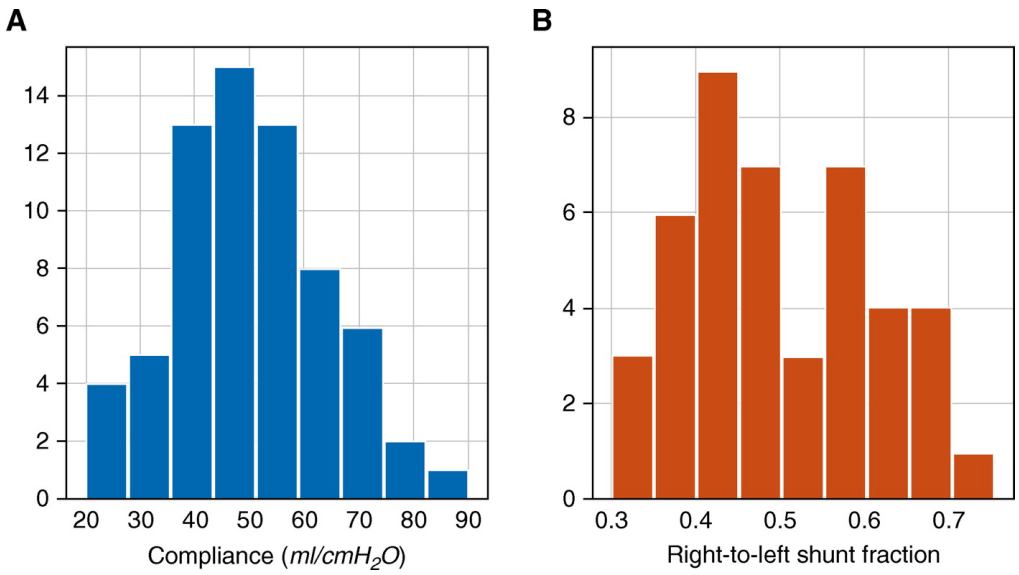


Figure 3. (A) Distributions of the observations of the compliance values observed in our cohort of patients. (B) Distributions of the observations of the right-to-left shunt values observed in our cohort of patients.[10]

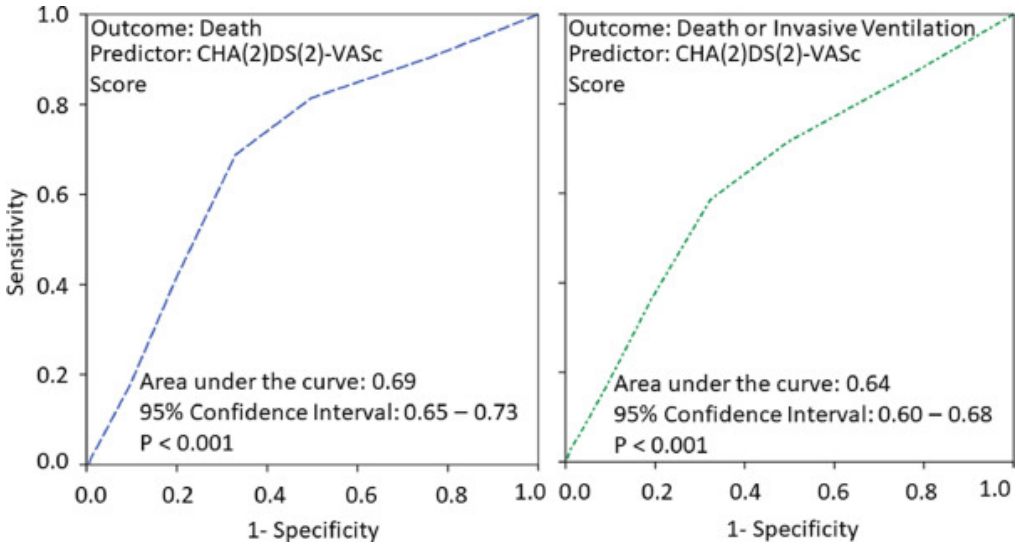


Figure 4. Receiver Operating Characteristic curves for death and the composite end point of death or invasive ventilation for the predictor of CHA(2)DS(2)-VASc score (ROC curve analysis was employed to quantify the prognostic power of CHA(2)DS(2)-VASc score for death and also for the composite end point (death and/or receiving invasive ventilation).[9]

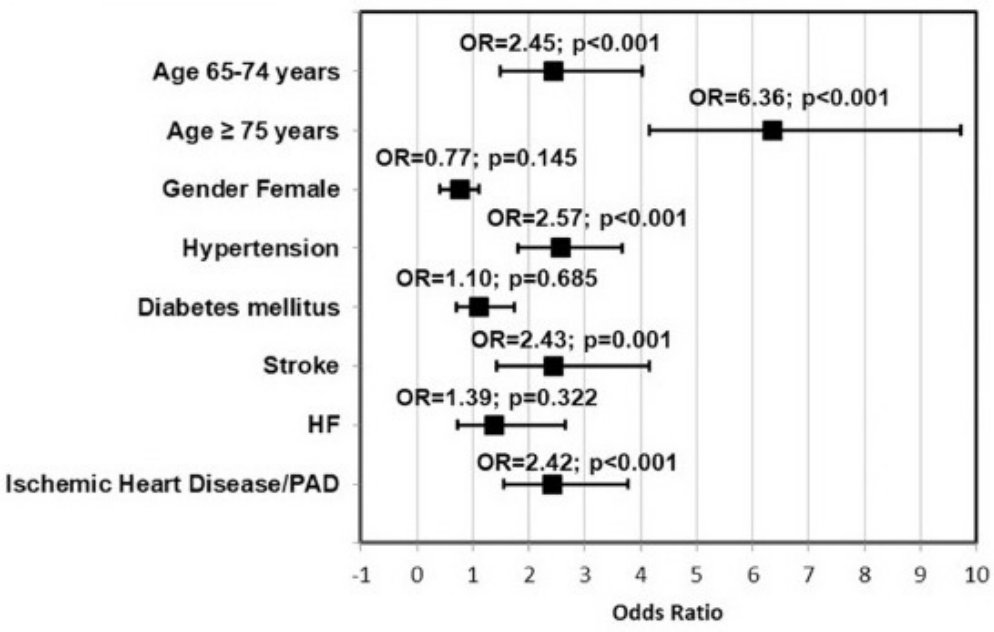


Figure 5. Forest plot of odds ratios for mortality of individual CHA(2)DS(2)-VASc components (crude OR for death for individual CHA(2)DS(2)-VASc components: age category, gender, hypertension, diabetes mellitus, ischemic heart disease, stroke, and heart failure).[9]

that combined cardiopulmonary alteration leads to a low pulmonary vascular resistance with blunted hypoxic vasoconstriction, which leads to post-capillary pulmonary hyptertension. So, it's very important to take into account the interaction between the lung and heart. Indeed, we published this paper in the *Journal of the American College of Cardiology*, looking at the echocardiography problems and abnormalities, both left ventricle wall motion and global dysfunction, but also right ventricular dysfunction.[12] Almost all of the patients have some echocardiography abnormality; myocardial injury is very common in patients with COVID-19. It's very important to perform echocardiography because echocardiography abnormalities are related with an odds ratio of almost 4 in terms of mortality (**Figure 6**), so it's very important to have a cardiologist in your unit looking for abnormalities of heart wall motion in particular.

(21) These are postmortem findings in patients in Bergamo (**Figure 7**), which is the epicenter of the epicenter in Lombardy.[13] We looked at the coagulation problems, and what we found is that is important to look at von-Willebrand factors and ADAMST13 axis.[14] And the increase in the imbalance of this ratio is important because this is a measure of hypercoagulable state and the risk of microthrombosis in COVID-19 patients. So, clearly there is something at the level of endothelium that leads to microthrombosis, which eventually leads to thromboembolism.

(22) We published a paper in the *European Respiratory Journal*, examining the interaction between respiratory failure and hypertension.[15] What we found is that most of our patients develop hypertension during the course of COVID, and the hypertension is related to the severity of respiratory failure and mortality (**Figure 8**). Following this paper, we decided to examine the effect of canrenone and spironolactone as possible treatments for hypertension in these patients. And indeed, we found that the use of this kind of antihypertensive drug is important because the there is clinical improvement and reduced chance of mortality in COVID-19 patients.[16] This is just a few patients; we still need a confirmation. We are planning to have a randomized study on the use of canrenone, and we will see the results, I hope, in the next few months.

(23) The other problem is inflammation. As I said, after the first two weeks of March, we decided to start the use of steroids and anti-inflammatory drugs, using a combination of methylprednisolone and anakinra, which is an anti-interleukin 1 drug. This is a retrospective analysis of our our results (**Figure 9**), and you can see that there is a clear difference using methylprednisolone and anakinra compared to patients in standard care treatment.[17] It seems, therefore, that steroids plus or minus anti-interleukin 1 puts the patient at an advantage compared to an anti-interleukin 6, because in this case, the activity of anakinra is short, so you can stop the treatment if there is any compromising effect on the immunocompetency of your patient. And it seems to work very well.

(24) As a center for lung transplantation, we suffer very much from COVID because we have had a reduction by half in the number of lung transplantations in our unit; we dropped from almost 40 to less than 20 lung transplantations, and this was related to the lack of donors. And on the other hand, we have some patients with COVID-19 after lung transplantation. This is the first report on the first four cases we recorded in our unit, and three of them have a very benign short-term outcome.[18] Unfortunately, one of these patients died, and the pathological result was that apparently COVID was the trigger for an allograft dysfunction, probably inducing rejection in our patient.

(25) For our Genomewide Association Study we put together our patient population with a Spanish population from Barcelona, Madrid, and San Sebastian and looked into a gene-wide association for severe COVID-19 respiratory failure.[19] We found two loci that are important for genetic susceptibility to COVID.[1] One is on chromosome 3, and one was related to the ABO blood group system. A is the worst outcome—the highest risk—B intermediate risk, and O the best outcome. And listed on the left are other interesting genes that are mainly related to the response to the virus and expression of ACE-2 on the cells. So this seems to be related to the possibility and the response to virus. And there is clearly an association with different alleles.

(26) So in conclusion, COVID-19 has been a rocket stimulus for health care in terms of management, new technology and new therapies. We had to consider how to deal with the disease and how to manage trying to standardize our approach to the disease. On the other hand, we looked to different approaches, in terms of ventilation, using prone and lateral positioning for patients with non-invasive ventilation or CPAP. Certainly, the ideas concerning different phenotypes of COVID-19 are interesting. We have had a lot of discussion about this, but certainly it is still important to study the physiology and pathophysiology of the disease, and certainly new studies are very welcome. New therapies are important; the use of a control of hypertension seems to be important. Certainly, anti-inflammatory drugs are important to control inflammation, knowing that the so-called cytokine storm seems to be important in terms of outcome, so controlling inflammation seems to be critical for our patients. And then we identified some genes that can be activated and can be means to identify the different responses to the disease in differ-

[1]See Genomewide Association Study of Severe Covid-19 with Respiratory Failure. N Engl J Med **2020**; 383:1522–1534. Available at: http://www.nejm.org/doi/10.1056/NEJMoa2020283.[19]

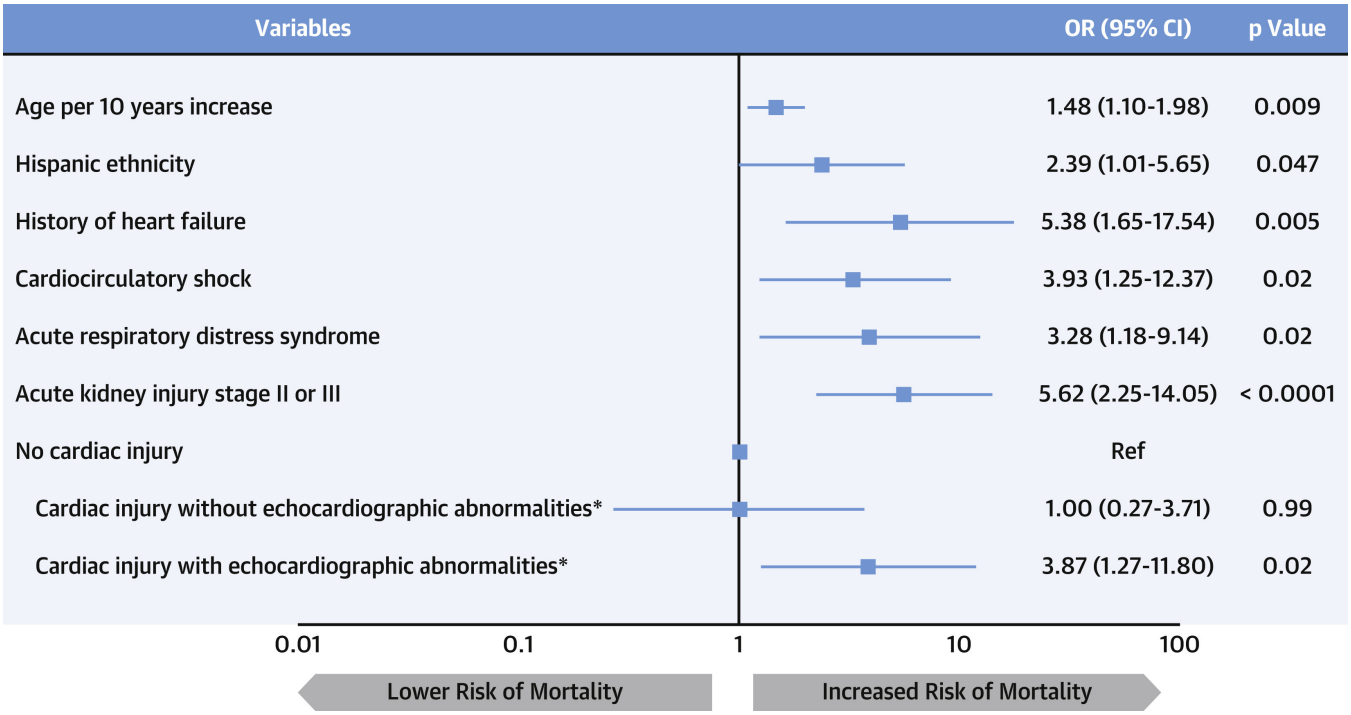


Figure 6. Independent predictors of in-hospital death from multivariable logistic-regression analysis.[12]

Reprinted from the *Journal of the American College of Cardiology*, Vol. 76, Gennaro Giustino, Lori B. Croft, Giulio G. Stefanini, Renato Bragato, Jeffrey J. Silbiger, Marco Vicenzi, Tatyana Danilov, Nina Kukar, Nada Shaban, Annapoorna Kini, Anton Camaj, Solomon W. Bienstock, Eman R. Rashed, Karishma Rahman, Connor P. Oates, Samantha Buckley, Lindsay S. Elbaum, Derya Arkonac, Ryan Fiter, Ranbir Singh, Emily Li, Victor Razuk, Sam E. Robinson, Michael Miller, Benjamin Bier, Valeria Donghi, Marco Pisaniello, Riccardo Mantovani, Giuseppe Pinto, Irene Rota, Sara Baggio, Mauro Chiarito, Fabio Fazzari, Ignazio Cusmano, Mirko Curzi, Richard Ro, Waqas Malick, Mazullah Kamran, Roopa Kohli-Seth, Adel M. Bassily-Marcus, Eric Neibart, Gregory Serrao, Gila Perk, Donna Mancini, Vivek Y. Reddy, Sean P. Pinney, George Dangas, Francesco Blasi, Samin K. Sharma, Roxana Mehran, Gianluigi Condorelli, Gregg W. Stone, Valentin Fuster, Stamatios Lerakis, Martin E. Goldman, Characterization of myocardial injury in patients with COVID-19, Pages 2043–2055, Copyright (2020), with permission from the American College of Cardiology Foundation.

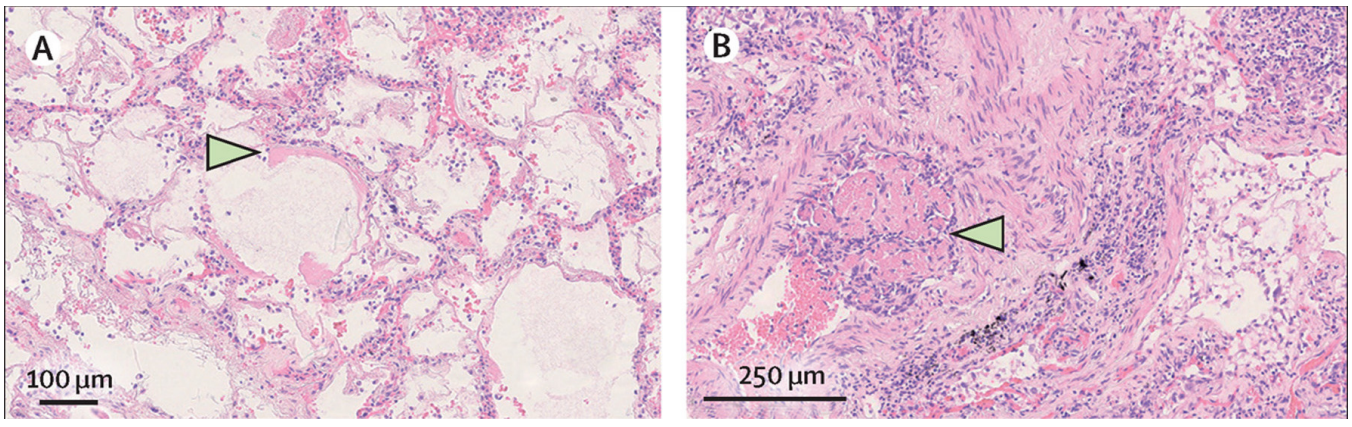


Figure 7. Haematoxylin and eosin-stained sections from representative areas of lung parenchyma with diffuse alveolar damage. (A) Exudative phase of diffuse alveolar damage with hyaline membranes (arrow). (B) Organising microthrombus (arrow).[13]

Reprinted from *The Lancet Infectious Diseases*, Vol. 20, Luca Carsana, Aurelio Sonzogni, Ahmed Nasr, Roberta Simona Rossi, Alessandro Pellegrinelli, Pietro Zerbi, Roberto Rech, Riccardo Colombo, Spinello Antinori, Mario Corbellino, Massimo Galli, Emanuele Catena, Antonella Tosoni, Andrea Gianatti, Manuela Nebuloni, Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: a two-centre descriptive study, Pages 1135–1140, Copyright (2020), with permission from Elsevier.

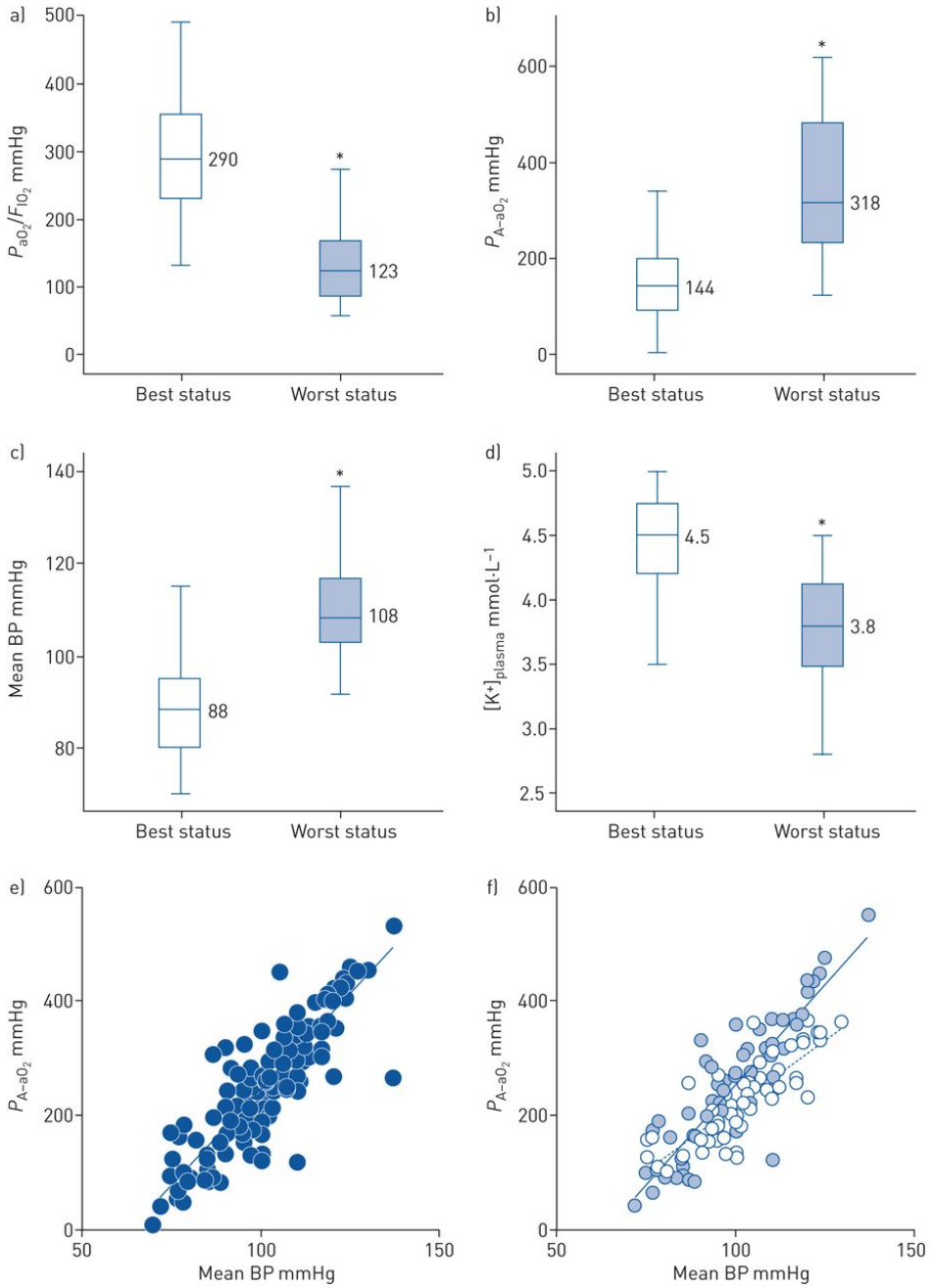
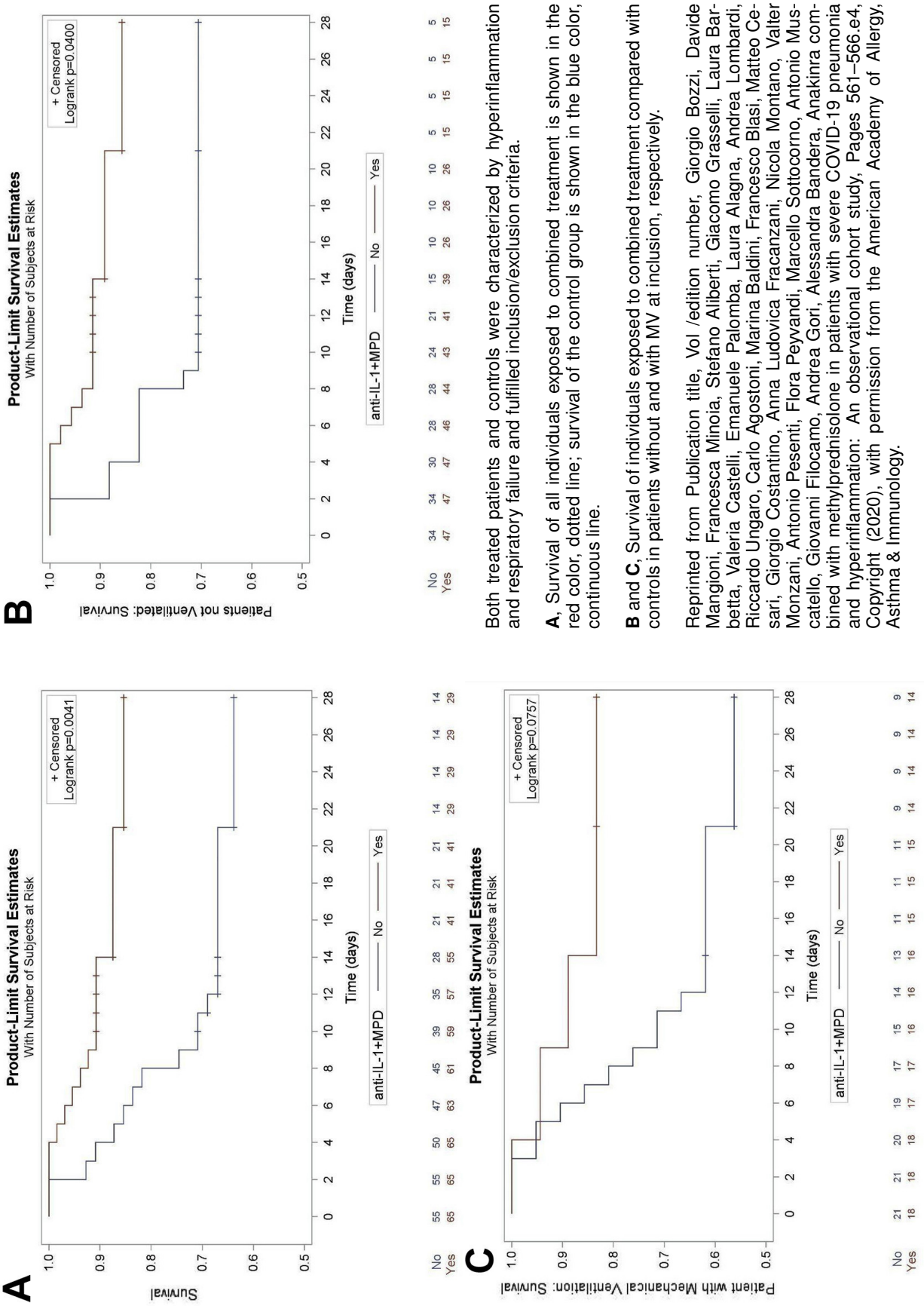


Figure 8. Box plots of a) oxygen and inspiratory fraction of oxygen ratio, b) alveolar-arterial oxygen gradient, c) mean blood pressure (BP) and d) plasma potassium levels ($[K+]_{plasma}$). Statistical significance was obtained through Mann-Whitney U-test comparing best status with worst status. *: $p<0.001$. e) Poon's analysis of $P_A - a_{O_2}$/mean BP: n=137, slope=6.666, R^2=0.757; $p<0.0001$. f) Poon's analysis of $P_A - a_{O_2}$/mean BP according to $[K+]_{plasma}$ stratum. In (f) pale blue dots represent the group with $[K+]_{plasma} \leq 3.8$mmolL^{-1} (n=78; slope=6.686, R^2=0.774; $p<0.0001$) and white dots represent the group with $[K+]_{plasma} > 3.8$mmolL^{-1} (n=59; slope=4.491, R^2=0.670; $p<0.0001$). $P_{a_{O_2}}$: arterial oxygen tension; F_{IO_2}: inspiratory oxygen fraction; $P_A - a_{O_2}$: alveolar-arterial oxygen tension difference.[15]

The liaison between respiratory failure and high blood pressure: evidence from COVID-19 patients
Marco Vicenzi, Roberta Di Cosola, Massimiliano Ruscica, Angelo Ratti, Irene Rota, Federica Rota, Valentina Bollati, Stefano Aliberti, Francesco Blasi. European Respiratory Journal 2020 56: 2001157; DOI: 10.1183/13993003.01157-2020



Both treated patients and controls were characterized by hyperinflammation and respiratory failure and fulfilled inclusion/exclusion criteria.

A, Survival of all individuals exposed to combined treatment is shown in the red color, dotted line; survival of the control group is shown in the blue color, continuous line.

B and **C**, Survival of individuals exposed to combined treatment compared with controls in patients without and with MV at inclusion, respectively.

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Figure 9. Survival according to treatment with anakinra and MPD (anti–IL-1 + MPD).[17]

ent patients. So, a lot of studies still to go, and we're still waiting for new information and new evidence that can lead us to better management and health care. So, I want to thank you for your attention.

DR. RAMIREZ

(27) Well, thank you. An excellent overview; a lot of things to discuss. Let me ask you a couple of things based on this very interesting presentation. The concept of hypertension—because I noticed that you have on a slide that hypertension is the most common comorbidity that you notice in your group. It's interesting; it has been our most common comorbidity here in Louisville. So two questions: firstly, you have your prior work with pneumonia, pneumococcal pneumonia—how do you connect the prior research of pneumonia with COVID pneumonia and hypertension? And then, you mentioned the two types of hypertension; what is the difference between the patient that arrived with hypertension as a comorbidity (that is the most common comorbidity) and the patient that develops hypertension during the hospitalization?

DR. BLASI

(28) Well, I must say that looking into pneumonia, I never thought of hypertension as a risk factor before. We know that cardiovascular diseases like myocardial infarction are more probable in pneumonia than in other diseases coming to the hospital. We are looking into the possibility that in some way, the infection that is related to the ACE-2 receptor can act on the aldesterone problems and pathway, so in some way, there can be an equilibrium between the renin and angiotensin pathway and aldosterone levels that can lead to hypertension. And so, the idea to use canrenone as a possible drug started from the this kind of pathophysiology hypothesis. We are looking into this pathway, and I think we will have the data in the next few weeks because we have samples from our patients' blood, and we are looking at the levels of angiotensin, renin, and so on and trying to understand if there is any problem between the admission and the patient who develops hypertension during the hospitalization—if it is any problem in this axis, and we're trying to understand the the pathophysiologic basis of hypertension in this patient.

DR. RAMIREZ

(29) Talking about our prior experience with pneumonia, again, as you alluded, hypertension was never too much of a comorbidity. But in other forms of pneumonia, probably one of the primary causes was smoking and COPD. But I notice that in your data, COPD is almost non-existent. And again, I see the same in our data here in Louisville. Why is it that COPD and smoking—all these things that cause chronic lung disease—don't seem to play such a critical role here. We have it with pneumococcus or with other with other forms of pneumonia; what do you make of it here?

DR. BLASI

(30) There's no good explanation. One possibility is that steroids could be involved. If you consider asthmatic patients, you have some effects where they have a reduction, but severe asthmatics are not at a low incidence of COVID. Maybe it's related to biologicals or to the kind of inflammation and the use of steroids. The number of patients coming to the hospital with the comorbidity of COPD is not as high as expected, but if a patient with COPD comes to the hospital with COVID, the outcome may be worse than for other patients. I don't have a very good explanation for this. We are seeing the same for our patients with bronchiectasis; we don't have a lot of patients with bronchiectasis or cystic fibrosis come into the hospital with COVID, but this may be related to the fact that these patients are used to being very cautious. They use masks, they stay at home, avoiding contact with other people, so it's easier to explain why bronchiectasis and cystic fibrosis patients have a lower incidence of COVID than expected, but for COPD, it is very difficult to understand why. It may relate to the use of steroids, but I don't know what the explanation is.

DR. RAMIREZ

(31) Let me ask you another question about the pathophysiology. Do you think that that that COVID pneumonia or the SARS-CoV-2 will get into the oropharynx via aspiration, inhalation, pneumonia with hematogenous spread—some people suggest even the possibility of some form of auto-immune disease—what is running through your mind when you discuss with your group, what would be the pathophysiology, how is it that these patients develop COVID pneumonia; are there really two types of ARDS—one type that progresses into another one—what is your your thought process regarding this at this moment?

DR. BLASI

(32) Well, looking to the receptors for the virus—along the airways you have receptors everywhere. Usually inhalation is the means of passing from the mouth to the lung. What happened then, I think, is a matter of individual response in terms of inflammation, the number of receptors, maybe related to the viral loads. It is not very clear what happened. What we see is that when the patient comes to the hospital, 7–10 days after the onset of symptoms, usually the virus is no longer the main problem. Rather, inflammation is the main problem.

(33) What we saw in March last year is that when we

started to use steroids, our patients' outcomes changed. We started steroids because our pulmonologists looked into the lungs and noticed their ground glass appearance, and we theorized that inflammation was significant, so we started to use steroids, despite the fact that at the time, the WHO said not to use steroids, because it's a viral infection. I think that the pathophysiology is probably related to the number of receptors, maybe the genetics because we found that there are differences in terms of severity according to different gene expressions, and the level of inflammation. We know that in pneumonia, inflammation is significant; your group has published a lot of papers on this. It's not just the question of bacterial versus viral infection. So, probably, there is a different response in different subjects, and so I think it's a very complex problem.

DR. RAMIREZ

(34) But definitely, you've seen decreased mortality with the use of steroids, usually?

DR. BLASI

(35) Absolutely. We published a paper some years ago with Marco Confalonieri in the Blue Journal, and we used the same approach with steroids.[20] In some patients, we also use a pulse of steroids to reduce inflammation—so, using a very high dose for three days, and then decreasing, like we do for rejection in lung transplantation. And this is a decision patient by patient; if there is no response, or if there is an increase in the ground glass appearance, we start with the high dose. We know very well that this approach is risky in many ways because when you use a high dose of steroids, there are many potential problems. Now we use dexamethasone for many patients because we have a protocol for it, but I think that in about half of our patients, we move from dexamethasone to methylprednisolone on high dose, and we get a response.

DR. RAMIREZ

(36) You have experience with lung transplantation during the pandemic; what criteria would you use to determine that a patient may be a candidate for lung transplantation?

DR. BLASI

(37) Well, we transplanted two patients. One was a young patient, 18 years old, who was intubated in another hospital. The situation was bad: there was no possibility of improvement, the lung was completely destroyed, so the hospital asked us to consider the possibility of lung transplantation. We had a multidisciplinary discussion—a couple of days' discussion; we analyzed everything because of the presence of COVID. We had to induce immunosuppression, so we decided to make a plasma treatment, and then we decided to try lung transplantation, and this guy is still alive and in good condition; he was transplanted in April of last year, and he's still doing very well. The other was a 49-year-old guy, the same situation in our hospital, but in this case, the transplantation was a disaster. After the lung transplantation he was intubated again—it was not possible to avoid intubation—and he died after two months of intubation. So, our experience is not so good. I have seen some reports around the world, for instance in China, four people were transplanted, three of them went well, and one died. I think we don't really have enough experience to say anything definitive. For us, it was really an emergency decision; it wasn't based on solid criteria.

DR. RAMIREZ

(38) I understand. Then this 18-year-old was not having multi-organ failure; it was mostly concentrated in the lung?

DR. BLASI

(39) Yes, his heart, kidney, and liver were all working, but the lung was completely destroyed. So we decided that there was no major problem in terms of lung transplantation, and our surgeon and intensivist decided to go for it, and it was a good decision. The other patient had kidney failure, and this was the main problem, I think, because he was on dialysis, and it was not a good idea to transplant him.

DR. RAMIREZ

(40) This has been a lot of lessons learned, and I like your concept that since this is a new disease, there is no evidence base, so experience is critical, along with the multidisciplinary approach and the standardization. In the last couple of minutes, I would like to ask: looking at 2021, you eluded to the concept of what would be the "COVID fatigue." How do you see this, and what is the way to move forward? Because as these new waves keep coming all over the world, I can see that the COVID fatigue is going to be a universal problem.

DR. BLASI

(41) In the first wave, when we opened the unit, we all felt like heroes working against the virus, and we were a very strong team working together, nurses, physiotherapists, cardiologists, respiratory disease. Then we had a couple of months working as pulmonologists, rather than COVID specialists, and then we had to reopen the unit, and it was extremely difficult, because of the idea of another year with COVID working on this kind of patient, seeing people dying with a really high frequency (around 20%). So we started with psychological support; I have three or four of my co-

workers going regularly to the psychologist, and I meet with each of them because I think that having an exchange of experience is important. And now we are meeting all together every week, trying to restart our souls, as it were. It's also related to the fact that in the first wave, the Italian population saw physicians and nurses as heroes. Now, they are starting to say, "well, you didn't do exactly what you had to do." So I asked my lawyer to look into this [*laughs*]. So, psychological support is very important, particularly in the second wave because the fatigue is definitely there.

DR. RAMIREZ

(42) This is very good experience and very good advice. Before I let you go, I need to ask whether you think the vaccines are going to fix any of these problems because I can see that the vaccine will help us to not get COVID, but as you say, going to the unit and having 20% mortality and being separated from the patient with all this protective equipment—I don't think the vaccine is going to resolve this. How do you see the vaccine? How is the vaccine going in your area, in Milan, and how do you see the vaccine for this coming year?

DR. BLASI

(43) Well, I think it will take about one year to vaccinate the Italian population, considering that we plan to vaccinate all people over 16—that means about 45 million people, which is not an easy task. I was one of the first in December to be vaccinated, and I'm expecting the second dose in a couple of days. I think the key point is that the vaccines will reduce the pressure on the hospital a little, because if we can prevent the most severe cases in the elderly, it would be a great help in controlling the situation. Our problem right now is that our emergency room is full of people with COVID, and we don't have time to care for the other (COVID-negative) patients with myocardial infarction, COPD or asthma exacerbation. So I think that what we expect from the vaccine is some reduction in pressure, not a complete solution to the problem. I think that this disease will become endemic in some way, like Legionella, for example. But the important thing is to reduce the pressure on the health system, and there are logistical problems because vaccinating so many people is very difficult. Our system is not ready because this is the first time we have had to vaccinate 45 million people, and it's clearly weird to think about how to deal with this. We started with health workers, but that's very easy because they are in the hospital; each hospital is vaccinating its own staff. But then we have to go outside into the community and try to vaccinate 100,000 people a week or more.

DR. RAMIREZ

(44) Well, let me say that this was a great conversation. Thank you for accepting our invitation. As we discussed, this is not the same as our face-to-face international meetings, but let's hope that at least the vaccination is going to resolve this issue and we can be face-to-face in a meeting in a couple of months. But yes, a lot of challenges, a lot of things to learn. Thank you for your time, and I will keep in contact.

DR. BLASI

(45) Thank you very much; it was a really great time for me.

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Appendix: Large Tables

Table 4. Demographic and clinical characteristics of patients in the first 24 hours of ICU admission for COVID-19 in Lombardy, Italy.[1]

	Patients by age, y, No. (%)								
	All	0–20	21–40	41–50	51–60	61–70	71–80	81–90	91–100
No. (%)	1591 (100)	4 (<1)	56 (4)	143 (9)	417 (27)	598 (38)	341 (21)	21 (1)	1 (<1)
Age, medium (IQR), y	63 (56-70)	16 (14-19)	34 (31-38)	47 (44-49)	56 (54-59)	65 (63-68)	74 (72-76)	83 (81-84)	91
Males	1304 (82)	3 (75)	44 (79)	119 (83)	355 (83)	484 (81)	279 (82)	19 (90)	1 (100)
Females	287 (18)	1 (25)	12 (21)	24 (17)	72 (17)	114 (19)	62 (18)	2 (10)	0
Comorbidities, No. with data	1043	3	35	82	273	380	253	1	1
None	334 (32)	0	23 (66)	50 (61)	107 (39)	107 (28)	47 (19)	0	0
Hypertension	509 (49)	0	4 (11)	21 (26)	121 (44)	195 (51)	156 (62)	12 (75)	0
Cardiovascular disease[a]	223 (21)	0	1 (3)	4 (5)	43 (16)	87 (23)	81 (32)	6 (38)	1 (100)
Hypercholesterolemia	188 (18)	0	1 (3)	2 (2)	30 (11)	92 (24)	59 (23)	5 (31)	0
Diabetes, type 2	180 (17)	0	1 (3)	4 (5)	40 (15)	86 (23)	46 (18)	3 (19)	0
Malignancy[b]	81 (8)	0	0	2 (2)	10 (4)	33 (9)	33 (13)	3 (19)	0
COPD	42 (4)	0	1 (3)	0	8 (3)	13 (3)	5 (2)	1 (6)	0
Chronic kidney disease	36 (3)	0	0	2 (2)	10 (4)	17 (4)	7 (3)	0	0
Chronic liver disease	28 (3)	0	0	2 (2)	8 (3)	13 (3)	5 (2)	0	0
Other[c]	205 (20)	3 (100)	6 (17)	10 (12)	49 (18)	77 (20)	55 (22)	5 (31)	0
Respiratory support, No.	1300	2	46	108	351	487	287	18	1
Invasive mechanical ventilation	1150 (88)	2 (100)	37 (80)	87 (81)	315 (90)	449 (92)	246 (86)	14 (78)	0
Noninvasive ventilation	137 (11)	0	8 (17)	16 (15)	33 (9)	36 (7)	39 (14)	4 (22)	1 (100)
Oxygen mask	13 (1)	0	1 (2)	5 (5)	3 (1)	2 (¡1)	2 (1)	0	0
PEEP, cm H_2O									
No.	1017	2	33	81	278	377	234	11	1
Median (IQR)	14 (12-16)	9.5 (5-14)	14 (10-15)	14 (12-15)	14 (12-15)	14 (12-16)	14 (12-15)	12 (8-15)	10
FiO_2, %									
No.	999	2	31	81	270	375	228	11	1
Median (IQR)	70 (50-80)	40 (30-50)	60 (50-70)	60 (50-80)	65 (50-80)	70 (55-80)	70 (50-80)	60 (50-90)	60
PaO_2/FiO_2 ratio									
No.	781	2	26	58	213	306	169	7	0
Median (IQR)	160 (114-220)	259 (195-323)	201.5 (123-248)	168.5 (112-260)	163 (120-230)	152.5 (110-213)	163 (120-205)	150 (86-250)	NA
Prone position, No./total (%)	240/875 (27)	0/2	3/25 (12)	24/71 (34)	70/247 (28)	90/337 (27)	51/187 (27)	2/6 (33)	NA
ECMO, No./total (%)	5/498 (1)	NA	0/15	0/42	2/149 (1)	3/193 (2)	0/95	0/4	NA

[a] Cardiovascular disease includes cardiomyopathy and heart failure. [b] Malignancy includes active neoplasia and neoplasia in remission. [c] Other includes anemia, asthma, inflammatory bowel disease, epilepsy, chronic respiratory insufficiency, endocrine disorders, connective tissue diseases, neurologic disorders, chronic pancreatitis, immunocompromise, and organ transplant. **Abbreviations:** COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation; FiO_2, fraction of inspired oxygen; ICU, intensive care unit; IQR, interquartile range; NA, not applicable; PaO_2, arterial partial pressure of oxygen; PEEP, positive-end expiratory pressure.

Table 5. Healthcare professionals involved in the multidisciplinary team.[3]

Respiratory physician	Initial evaluation of patient Choice of respiratory support Evaluation and placement of central venous catheter and/or arterial catheter Identify signs of sepsis or multi-organ failure Setting of sedative therapy, nutritional therapy, anti-thrombotic prophylaxis, hydration, antiviral and antibiotic therapy
Fellow	Initial evaluation of patient Placement of arterial catheter Blood and microbiological tests request Arterial blood gas test Pneumonia follow-up with lung ultrasound
Nurse	Preparation of medical devices to support respiratory insufficiency EKG Placement of peripheral venous catheter Placement of bladder catheter Collection of vital parameters Therapies administration
Respiratory physiotherapist	Evaluation with respiratory physician of ventilator/oxygen support Early mobilization
Cardiologist	Evaluation and placement of central venous catheter and/or arterial catheter Identification and management of cardiac complications Anti-hypertensive therapy Inotropic support
Infectious disease specialist	Identification of patients candidate to anti-viral or anti-inflammatory therapy Choice of antiviral drugs Choice of antibiotic therapy Identification and treatment of sepsis Super-infection identification and management
Rheumatologist	Identification of patients candidate to the anti-inflammatory and specific anti-cytokine treatment Definition of a tailored anti-inflammatory strategy according to the patient characteristics
Intensivist	Multidisciplinary discussion to early identify patients candidate to intensive care management DNI/DNR status

Abbreviations: *EKG* Electrocardiogram, *DNI* Do not intubate, *DNR* Do not resuscitate.

Table 6. Other therapies for patients with COVID-19 disease.[3]

Antipyretic	Paracetamol 1 g intravenous/orally every 8 h (with the goal to keep fever under control in patients with respiratory insufficiency) for all patients with body temperature $>$ 37℃.
	Alternative:Diclofenac 75 mg intravenous in 24 h.
	Metamizole 500 mg intravenous every 8 h.
Systemic hypertension treatment	Patients with systemic hypertension already on medication: antihypertensive therapy should be continued regardless of pharmacologic (ACE-inhibitor, sartan, beta-blocker). Diuretics should be discontinued to avoid hypovolemic status.
	Patients that develop systemic hypertension during the hospitalization: treatment options include potassium-spring diuretics (spironolactone 50 mg x 2/die or potassium canreonate intravenous with a minimum dose of 100 mg x 2/die) associated with ACE-inhibitors or sartans.
Hydration	Hydration should be considered in all patients (especially patients with fever).
	Before start of treatment with CPAP or NIV hydration should be provided in patients with signs of hypovolemia.
Nutrition	In patients that are able to eat in HFNC or nasal cannulas: self-sufficient oral feeding
	CPAP or NIV-dependent: nasal feeding tube should be placed to provide enteral feeding (e.g.: isosource protein 25 Kcal/kg)
	In selected cases parenteral feeding (after positioning of central arterial access):1. BMI $\geq$ 20 provide at least 1080 kcal (speed:1,5 ml/kg/h)
	2. BMI $<$ 20 provide at least 1540 kcal (speed:1,5 ml/kg/h)
Sedation	Anxious state: Alprazolam (starting dose 0,25 mg x 2/die orally)
	Psychomotor agitation, attempt to remove medical devices, tachypnoea: morphine bolus (2,5 mg i.v./s.c., max every 6 h) $\pm$ Alprazolam (starting dose 0,25 mg x 2/die). At least 2 h between administration of alprazolam and morphine.
End of life support	Starting dose: syringe pump with morphine 10 mg + midazolam 5 mg + haloperidol 5 mg + metoclopramide 10 mg
	Dose should be modified according to clinical condition of the patient
Gastric protection	Omeprazole 20 mg every 24 h orally/intravenous
Home therapy that should not be discontinued during hospitalization	Levothyroxine
	Beta-blockers and others essential cardiological therapies
	Insulin in diabetic patients (oral antihyperglycemic should be discontinued in case of P/F ratio $<$ 300 or acute kidney injury)
	Corticosteroid therapy (*decalage* should be encouraged based on clinical condition of underlying condition)