

## Supplementary appendix

**TITLE:** Clinical Characteristics, Risk Factors and Outcomes in Patients with Severe COVID-19 Registered in the ISARIC WHO Clinical Characterisation Protocol: A Prospective, Multinational, Multicentre, Observational Study.

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**Abbreviated running title:** Severe COVID-19 Cohort.

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Ribeiro, Maria Ines; Richardson, David; Richardson, Denise; Richier, Laurent; Riera, Jordi; Rios, Ana Lúcia; Rishu, Asgar; Rizer, Nicholas; Roberto, André; Roberts, Stephanie; Robertson, David L.; Robineau, Olivier; Roche-Campo, Ferran; Rodari, Paola; Rodeia, Simão; Roger, Pierre-Marie; Rojek, Amanda; Romaru, Juliette; Roncon-Albuquerque Jr, Roberto; Rosa-Calatrava, Manuel; Rose, Michael; Rosenberger, Dorothea; Rossanese, Andrea; Rossetti, Matteo; Rossignol, Bénédicte; Rossignol, Patrick; Rössler, Bernhard; Rousset, Stella; Roy, Carine; Roze, Benoît; Rusmawatingtyas, Desy; Russell, Clark D.; Ryckaert, Steffi; Rygh Holten, Aleksander; Saba, Isabela; Sadaf, Sairah; Sadat, Musharaf; Sahraei, Valla; Saint-Gilles, Maximilien; Salahuddin, Nawal; Salazar, Leonardo; Sales, Gabriele; Sallaberry, Stéphane; Salmon Gandonniere, Charlotte; Salvator, Hélène; Sanchez, Olivier; Sanchez-Miralles, Angel; Sancho-Shimizu, Vanessa; Sandhu, Gyan; Sandrine, Pierre-François; Sandulescu, Oana; Santos, Marlene; Sarfo-Mensah, Shirley; Sarmiento, Iam Claire E.; Sarton, Benjamine; Satyapriya, Sree; Saviciute, Egle; Schaffer, Justin; Schermer, Tjard; Scherpereel, Arnaud; Schneider, Marion; Schroll, Stephan; Schwameis, Michael; Scott, Janet T.; Scott-Brown, James; Sedillot, Nicholas; Seitz, Tamara; Semaille, Caroline; Semple, Malcolm G.; Senneville, Eric; Sepulveda, Claudia; Sequeira, Filipa; Sequeira, Tânia; Serpa Neto, Ary; Shadowitz, Ellen; Shamsah, Mohammad; Sharma, Pratima; Shaw, Catherine A.; Shaw, Victoria; Sheharyar, Ashraf; Shi, Haixia; Shiekh, Mohiuddin; Shime, Nobuaki; Shimizu, Hiroaki; Shimizu, Keiki; Shimizu, Naoki; Shrapnel, Sally; Shum, Hoi Ping; Si Mohammed, Nassima; Sibiude, Jeanne; Siddiqui, Atif; Sigfrid, Louise; Sillaots, Piret; Silva, Catarina; Silva, Maria Joao; Silva, Rogério; Sin, Wai Ching; Skogen, Vegard; Smith, Sue; Smood, Benjamin; Smyth, Michelle; Snacken, Morgane; So, Dominic; Solis, Monserrat; Solomon, Joshua; Solomon, Tom; Somers, Emily; Sommet, Agnès; Song, Myung Jin; Song, Rima; Song, Tae; Sonntagbauer, Michael; Soum, Edouard; Sousa, Ana Chora; Sousa, Marta; Sousa Uva, Maria; Souza-Dantas, Vicente; Sperry, Alexandra; Sri Darshana, B. P. Sanka Ruwan; Srisikandan, Shiranee; Stabler, Sarah; Staudinger, Thomas; Stecher, Stephanie-Susanne; Stienstra, Ymkje; Stiksrud, Birgitte; Streinu-Cercel, Anca; Streinu-Cercel, Adrian; Strudwick, Samantha; Stuart, Ami; Stuart, David; Suen, Jacky Y.; Suen, Gabriel; Sultana, Asfia; Summers, Charlotte; Surovcová, Magdalena; Syrigos, Konstantinos; Sztajn bok, Jaques; Szuldrzynski, Konstanty; Tabrizi, Shirin; Taccone, Fabio; Tagherset, Lysa; Taleb, Sara; Talsma, Jelmer; Tan, Le Van; Tanaka, Hiroyuki; Tanaka, Taku; Taniguchi, Hayato; Tanveer, Hussain; Tardivon, Coralie; Tattevin, Pierre; Taufik, M Azhari; Tedder, Richard S.; Teixeira, João; Tejada, Sofia; Tellier, Marie-Capucine; Teotonio, Vanessa; Téoulé, François; Terpstra, Pleun; Terrier, Olivier; Terzi, Nicolas; Tessier-Grenier, Hubert; Thibault, Vincent; Thill, Benoît; Thompson, MD, Shaun; Thomson, Emma C.; Thomson, David; Thuy, Duong Bich; Thwaites, Ryan S.; Timsit, Jean-François; Tirupakuzhi Vijayaraghavan, Bharath Kumar; Tissot, Noémie; Toki, Maria; Tolppa, Timo; Tonby, Kristian; Torres, Antoni; Torres-Zevallos, Hernando; Trapani, Tony; Treoux, Théo; Trieu, Huynh Trung; Tromeur, Cécile; Trontzas, Ioannis; Troost, Jonathan; Trouillon, Tiffany; Truong, Jeanne; Tual, Christelle; Tubiana, Sarah; Tuite, Helen; Turmel, Jean-Marie; Turtle, Lance C.W.; Twardowski, Pawel; Uchiyama, Makoto; Udayanga, PG Ishara; Udy, Andrew; Ullrich, Roman; Uribe, Alberto; Usman, Asad; Val-Flores, Luís; Valran, Amélie; Van De Velde, Stijn; van den Berge, Marcel; Van der Feltz, Machteld; Van Der Vekens, Nicky; Van der Voort, Peter; Van Der Werf, Sylvie; van Gulik, Laura; Van Hattem, Jarne; van Lelyveld, Steven; van Netten, Carolien; van Twillert, G; Vanel, Noémie; Vanoverschelde, oHenk; Vauchy, Charline; Veislinger, Aurélie; Ventura, Sara; Verbon,



Annelies; Vidal, José Ernesto; Vieira, César; Villanueva, Joy Ann; Villar, Judit; Villeneuve, Pierre-Marc; Villoldo, Andrea; Vinh Chau, Nguyen Van; Visseaux, Benoit; Visser, Hannah; Vitiello, Chiara; Vuotto, Fanny; Wang, Chih-Hsien; Wei, Jia; Weil, Katharina; Wesselius, Sanne; Wham, Murray; Whelan, Bryan; White, Nicole; Wicky, Paul Henri; Wiedemann, Aurélie; Wille, Keith; Williams, Virginie; Wils, Evert-Jan; Wolf, Timo; Xynogalas, Ioannis; Yacoub, Sophie; Yamazaki, Masaki; Yazdanpanah, Yazdan; Yelnik, Cécile; Yerkovich, Stephanie; Yokoyama, Toshiki; Yonis, Hodane; Yuliarto, Saptadi; Zaaqoq, Akram; Zabbe, Marion; Zacharowski, Kai; Zahran, Maram; Zambon, Maria; Zambrano, Miguel; Zanella, Alberto; Zoufaly, Alexander; Zucman, David.

## 2. Strobe Checklist

	Item No.	Recommendation	Section or Page in the manuscript
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	Title
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Background
Objectives	3	State specific objectives, including any prespecified hypotheses	Background, last paragraph
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	Methods
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Methods
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed	Methods, statistical analysis
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods
Bias	9	Describe any efforts to address potential sources of bias	Methods (statistical analysis) and limitation section in the discussion
Study size	10	Explain how the study size was arrived at	No sample size was calculated
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Methods
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Methods
		(b) Describe any methods used to examine subgroups and interactions	Methods
		(c) Explain how missing data were addressed	Methods
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed	Methods
		(e) Describe any sensitivity analyses	Methods and supplementary appendix
<b>Results</b>			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Results, first paragraph
		(b) Give reasons for non-participation at each stage	Results first paragraph
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Results, second paragraph
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	Methods
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	Results

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Results, subgroup section
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	Discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Limitation section at the end of the discussion
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion and Limitation section
Generalisability	21	Discuss the generalisability (external validity) of the study results	Limitation section
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	At the end of the methods
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Results
		(b) Report category boundaries when continuous variables were categorized	Results
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable

### 3. Supplementary tables

**Supplementary Table 1.** Generalised Additive Model (GAM) fitted to assess the association of being admitted to the intensive care unit (ICU) with 90-day mortality.

Variable	OR	95% CI		<i>p</i> value
		Lower	Upper	
ICU admission	0.69	0.64	0.74	<0.0001
High flow nasal cannula	1.08	1.02	1.14	0.005
Non-invasive respiratory support	1.38	1.31	1.45	<0.0001
Invasive mechanical ventilation	2.06	1.89	2.24	<0.0001
Vasopressors or inotropes	1.73	1.60	1.88	<0.0001
Comorbidities	1.08	1.07	1.10	<0.0001
Temperature on hospital admission	0.90	0.88	0.92	<0.0001
Heart rate on hospital admission	1.01	1.00	1.01	<0.0001
Respiratory rate on hospital admission	1.03	1.02	1.03	<0.0001
Systolic blood pressure on hospital admission	0.99	0.98	0.99	<0.0001
Diastolic blood pressure on hospital admission	0.99	0.98	0.99	<0.0001
Acute Respiratory Distress Syndrome	1.51	1.42	1.60	<0.0001
Male	1.26	1.20	1.32	<0.0001
Month of hospital admission	0.96	0.95	0.97	<0.0001
New cases per million	0.99	0.99	0.99	<0.0001
Age	Estimated marginal means	Lower	Upper	
20	7.4%	6.0%	9.1%	
40	9.7%	8.9%	10.7%	
60	21.7%	20.8%	22.6%	
80	55.5%	54.4%	56.6%	

**Supplementary Table 2.** Sensitivity analysis excluding patients enrolled in the United Kingdom. Generalised Additive Model (GAM) fitted to assess the association of being admitted to the intensive care unit (ICU) with 28-day mortality.

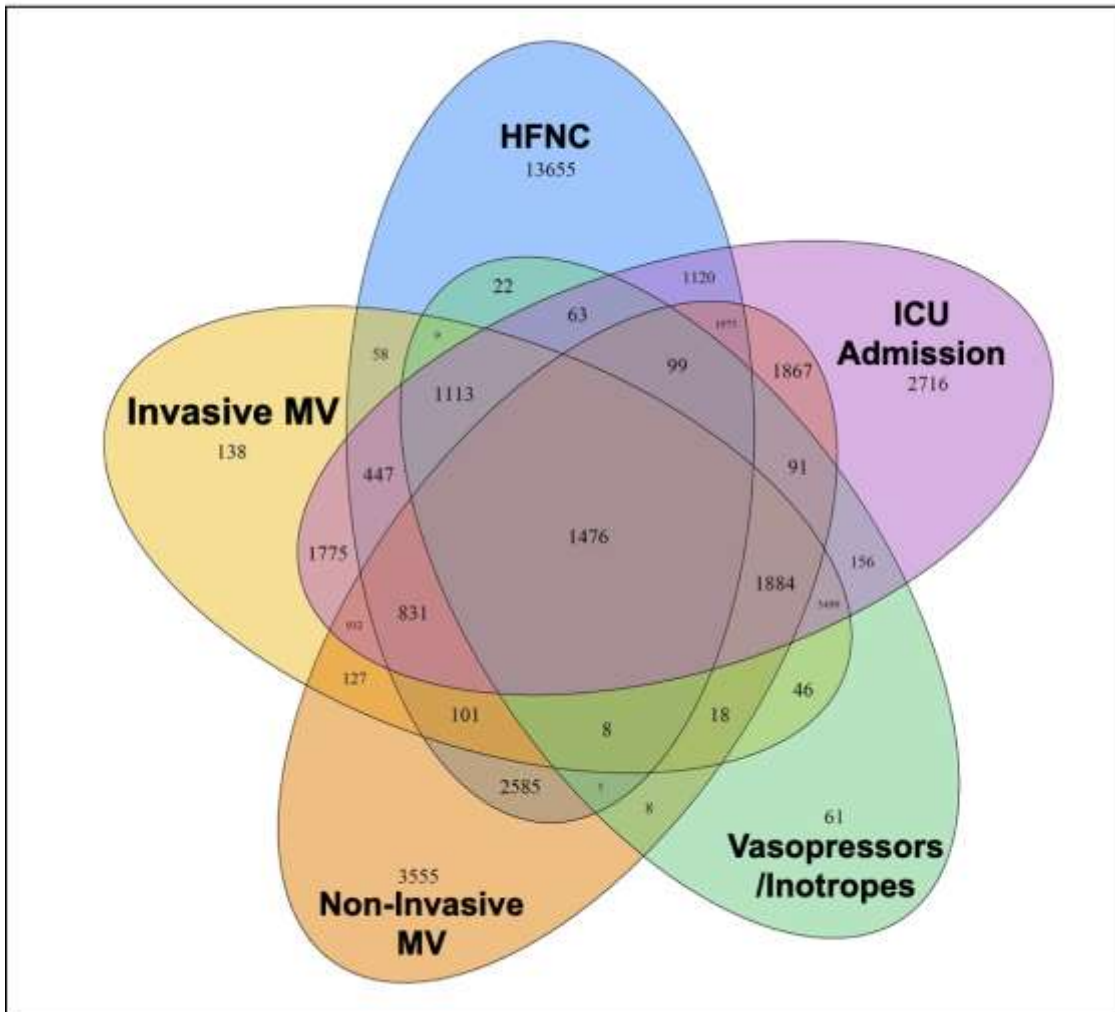
		95% CI		
Variable	OR	Lower	Upper	<i>p value</i>
ICU admission	0.69	0.65	0.75	<0.0001
High flow nasal cannula	1.05	0.9	1.11	0.052
Non-invasive respiratory support	1.37	1.31	1.44	<0.0001
Invasive mechanical ventilation	1.97	1.81	2.14	<0.0001
Vasopressors or inotropes	1.56	1.44	1.70	<0.0001
Comorbidities	1.07	1.06	1.09	<0.0001
Temperature on hospital admission	0.92	0.89	0.93	<0.0001
Heart rate on hospital admission	1.01	1.00	1.01	<0.0001
Respiratory rate on hospital admission	1.03	1.02	1.03	<0.0001
Systolic blood pressure on hospital admission	1.00	1.00	1.01	<0.0001
Diastolic blood pressure on hospital admission	0.99	0.98	0.99	<0.0001
Acute Respiratory Distress Syndrome	1.47	1.39	1.56	<0.0001
Male	1.25	1.19	1.31	<0.0001
Month of hospital admission	0.98	0.96	0.99	<0.0001
New cases per million	0.99	0.99	0.99	<0.0001
Age	Estimated marginal means	Lower	Upper	
20	10.1%	7.9%	12.9%	
40	12.8%	11.2%	14.6%	
60	20.4%	18.6%	22.3%	
80	42.7%	39.8%	45.7%	

**Supplementary Table 3.** Sensitivity analysis for ethnicity. Generalised Additive Model (GAM) fitted to assess the association of being admitted to the intensive care unit (ICU) with 28-day mortality.

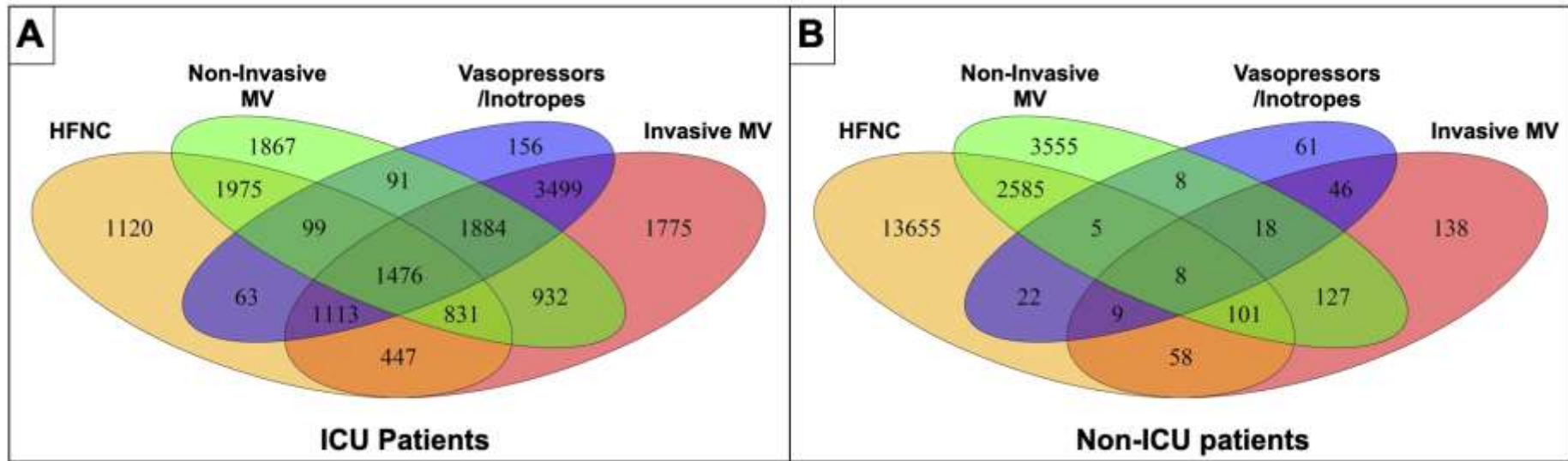
Variable	OR	95% CI		<i>p value</i>
		Lower	Upper	
ICU admission	0.60	0.56	0.65	<0.0001
High flow nasal cannula	1.02	0.97	1.08	0.052
Non-invasive respiratory support	1.24	1.18	1.30	<0.0001
Invasive mechanical ventilation	1.91	1.75	2.07	<0.0001
Vasopressors or inotropes	1.57	1.45	1.71	<0.0001
Comorbidities	1.08	1.07	1.10	<0.0001
Temperature on hospital admission	0.89	0.87	0.91	<0.0001
Heart rate on hospital admission	1.01	1.00	1.01	<0.0001
Respiratory rate on hospital admission	1.03	1.02	1.03	<0.0001
Systolic blood pressure on hospital admission	0.99	0.99	1.10	0.17
Diastolic blood pressure on hospital admission	0.99	0.98	0.99	<0.0001
Acute Respiratory Distress Syndrome	1.49	1.40	1.58	<0.0001
Male	1.20	1.14	1.25	<0.0001
Month of hospital admission	0.97	0.96	0.99	<0.0001
New cases per million	0.99	0.99	0.99	<0.0001
Age (>65 years old)	4.13	3.92	4.36	<0.0001
Asian	1.61	0.91	2.97	0.10
Black	1.26	0.71	2.34	0.43
White	1.53	0.87	2.81	0.14
Latino	0.84	0.46	1.63	0.60
Unknown	1.05	0.60	1.93	0.86

#### 4. Supplementary figures

**Supplementary figure 1.** Venn diagram presenting how treatments (i.e., High-flow nasal cannula, Invasive mechanical ventilation, non-invasive mechanical ventilation, vasopressors/inotropes, and admission to the intensive care) interact among patients included in the cohort.

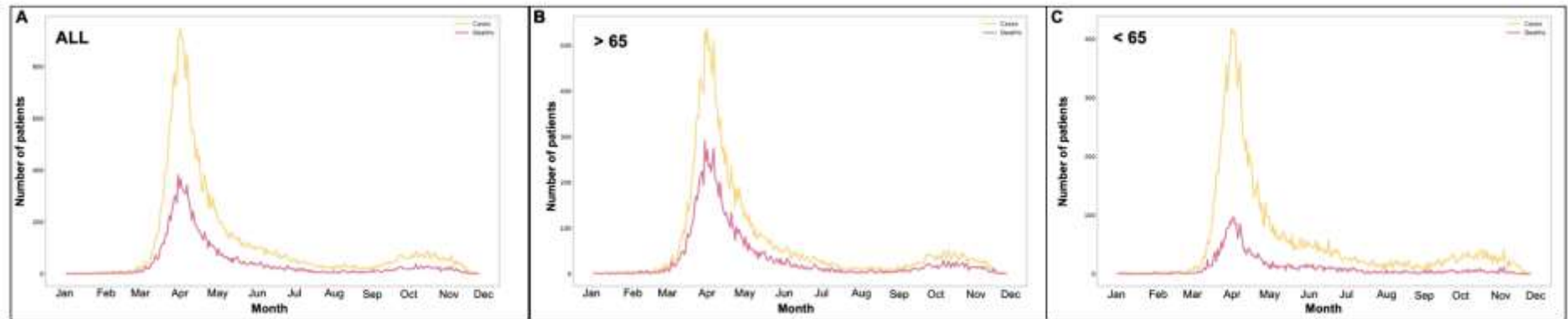


**Supplementary figure 2.** Venn diagram presenting how treatments (i.e., High-flow nasal cannula, Invasive mechanical ventilation, non-invasive mechanical ventilation, and vasopressors/inotropes) interact among patients included in the cohort, stratified by admission to the intensive care unit.

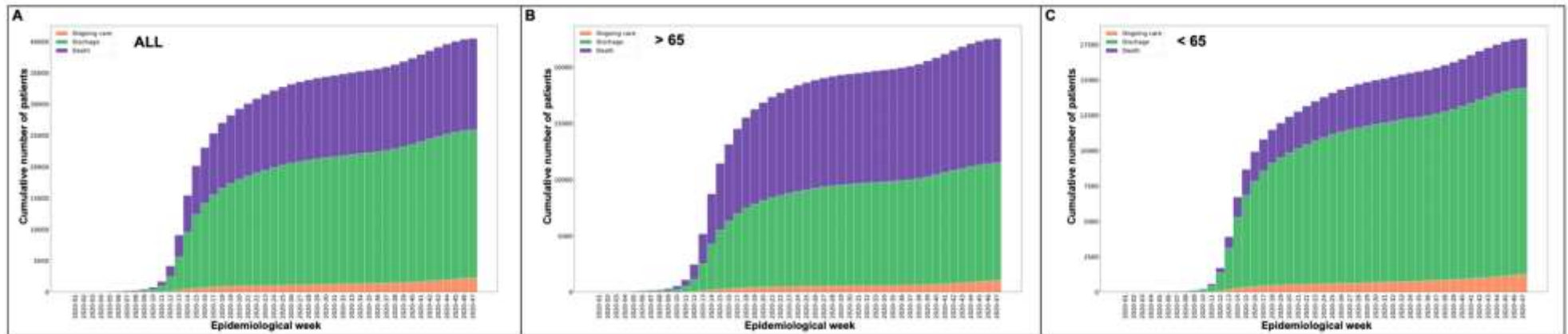




**Supplementary figure 3.** Histogram representing the number of new cases (in yellow) and the number of deaths (in red), in all patients (A), in patients older than 65 years old (B), and patients younger than 65 years old (C), during the study period.



**Supplementary figure 4.** Cumulative histogram presenting the number of patients discharged alive (green), patients who died (purple), and patients that remained hospitalised at the time of the data extraction. Panel, A represents all the patients included in the study, panel B patients older than 65, and panel C the patients younger than 65.



**Supplementary figure 5. Estimation of the non-linear effect on 90-day mortality using a Generalised Additive Model (GAM) in patients with severe COVID-19 stratified by Intensive Care Unit (ICU) admission.** Age is shown to be an essential factor for higher mortality in patients with severe COVID-19; however, patients admitted to the ICU have a lower mortality rate independently of the age (A). Even after adjusting by the number of new cases per million at the moment of hospital admission (B) and the interaction over time (C), the marginal 90-day mortality rate was lower in patients admitted to the ICU.

