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COVID-19: identifying the main outcome predictors. A retrospective cohort study in Northern Italy

S. GRECO[1], B. BONSI[1], A. BELLA[1], N. FABBRI[2], C. ROCCHI[3], M.E. BELLIO[3], L. MASSOLI[3], S. GIACCARI[3], M. GAVIOLI[3], M. FAZZIN[2], F. D'URBANO[5], E. ROSSIN[5], C.V. FEO[2,4], S. PARINI[3], G.N. CAVALLESCO[5], A. PASSARO[1,6]

[1]Department of Translational Medicine, University of Ferrara, Ferrara, Italy
[2]Surgery Department, Unit of General Surgery, Ospedale del Delta, Ferrara, Italy
[3]Medical Department, Unit of Internal Medicine, Ospedale del Delta, Ferrara, Italy
[4]Department of Medical Sciences, Unit of General Provincial Surgery, University of Ferrara, Ferrara, Italy
[5]Surgery Department, Unit of General Surgery, University Hospital of Ferrara Arcispedale Sant'Anna, Ferrara, Italy
[6]Medical Department, Unit of Internal Medicine, University Hospital of Ferrara Arcispedale Sant'Anna, Ferrara, Italy

Salvatore Greco and Beatrice Bonsi equally contributed to this article

Abstract. – OBJECTIVE: The need for efficient drugs and early treatment of patients with SARS-CoV-2 infection developing COVID-19 symptoms is of primary importance in daily clinical practice and it is certainly among the most difficult medical challenges in the current century. Recognizing those patients who will need stronger clinical efforts could effectively help doctors anticipate the eventual need for intensification of care (IoC) and choose the best treatment in order to avoid worse outcomes.

PATIENTS AND METHODS: We enrolled 501 patients, consecutively admitted to our two COVID hospitals, and collected their clinical, anamnestic and laboratory data on admission. The aim of this retrospective study was to identify those data that are strictly associated with COVID-19 outcomes (IoC and in-hospital death) and that could somehow be intended as predictors of these outcomes. This allowed us to provide a "sketch" of the patient who undergoes, more often than others, an intensification of care and/or in-hospital death.

RESULTS: Males were found to have a double risk of needing an IoC (OR=2.11) and a significant role was played by both the PaO_2/FiO_2 ratio on admission (OR=0.99) and serum LDH (OR=1.01). The main predictors of in-hospital death were age (OR=1.08) and the PaO_2/FiO_2 ratio on admission (OR=0.99).

CONCLUSIONS: Male patients with high serum LDH on admission are those who undergo more often an intensification of care among COVID-19 inpatients. Both age and respiratory performances on admission modify the prognosis within the hospitalization period.

Key Words:
COVID-19, SARS-CoV-2, Outcome prediction.

Abbreviations
ALT: Alanine Transferase; ARDS: Acute Respiratory Distress Syndrome; BNP: Brain Natriuretic Peptide; CCI: Charlson Comorbidity Index; COVID-19: COronaVIrus Disease 2019; CPK: Creatine Phosphokinase; CRP: C-Reactive Protein; eGFR: estimated Glomerular Filtration Rate; HS TnI: Troponin I HS; IQR: Interquartile Rang; ICUs: Intensive Care Units; iHDp: in-hospital Dead Patients; iHSp: in-hospital Survived Patients; IL-6: *Interleukin 6*; IoC: Intensification of Care; IoCp: Patients Needing the Intensification of Care; LDH: Lactic Dehydrogenase; MEWS: Modified Early Warning Score; nIoCp: Patients who did not undergo the Intensification of Care; SARS-CoV-2: Severe Acute Respiratory Syndrome CoronaVirus 2; STROBE: Strenghtening the Reporting of Observational Studies in Epidemiology; TIA: *Transient Ischemic Attack*; TNF: Tumor Necrosis Factor; WBC: White Blood Cells; 100-ddp: 100-day Dead Patients; 100-dsp: 100-day Survived Patients.

Introduction

COVID-19 (COronaVIrus Disease 2019) is an infectious disease caused by a new member of coronaviruses family, SARS-CoV-2 (Severe Acute Respiratory Syndrome CoronaVirus 2)[1] and, as of January 6th 2022, more than 298 million COVID-19 confirmed cases and 5.4 million deaths were reported in more than 200 countries and territories.

Corresponding Author: Angelina Passaro, MD, Ph.D; e-mail: angelina.passaro@unife.it

The disease usually involves adult subjects, more often between 30 and 79 years old, with a higher mortality rate in the elderly population[2,3]; this rate is even higher in comorbid patients with history of cardiovascular events, diabetes, chronic pulmonary pathologies, hypertension and any kind of tumor[4,5]. A Chinese study recently showed that patients with diabetes or hypertension have a doubled risk of developing the severe form of COVID-19 with a higher probability of admission to the Intensity Care Units (ICUs); this risk was even tripled for patients with previous cerebrovascular events. Pre-existing diabetes and hyperglycaemia were also found to be independent predictors of SARS-related death[6].

The clinical presentation of COVID-19 can be extremely heterogeneous: up to 80% of patients have mild influenza-like symptoms, while up to 15% of patients can outset with a severe form of pneumonia; 5% develop rapidly an acute respiratory distress syndrome (ARDS), with systemic hyperinflammation (cytokine storm) that can hesitate in systemic shock, multiorgan failure and death[7,8]. Fever is the most frequent symptom, and it appears in more than 90% of cases during hospitalization; cough is present in more than 65% of patients, while other atypical signs of systemic involvement, such as arthralgia, myalgia, asthenia, headache, upper respiratory tract symptoms and gastrointestinal symptoms (nausea and diarrhoea) can also occur. Smell and taste disorders (anosmia and dysgeusia) were described for the first time in a group of Italian patients[9], as possible signs of a central nervous system's involvement.

As for laboratory markers, a strong relationship between the white blood cells counts (WBC) and the clinical worsening exists, with higher lymphopenic rates in critical patients[4]. Serum inflammatory markers such as C-reactive protein (CRP) or ferritin, and organ-damage markers such as D-dimer, creatine phosphokinase (CPK), lactic dehydrogenase (LDH) or troponin I HS (HS TnI) are generally higher in critical patients and may be used as prognostic factors in the evolution of the critical phases[10,11]. COVID-19 is also associated with kidney disease, with higher serum creatinine levels and estimated glomerular filtration rates (eGFR) lower than 60 ml/min/1.73 m^2 in the first Chinese studies, where acute kidney failure occurred in 5% of cases[12].

It is reasonable to think that unchangeable factors (such as age and comorbidities), laboratory and clinical parameters are reliable predictors of short-term COVID-19 outcomes. Their periodic evaluation could be thus indicated for better diagnostic and prognostic frameworks in patients with the disease. The ability to accurately evaluate the risk factors associated with poor prognosis among SARS-CoV-2-infected patients is essential for an early intervention and for increasing the patients' chances of survival. Similarly, identifying patients at risk of developing the severe form of the disease could help clinicians better allocate their limited care resources[13].

In our study, we aimed at finding the personal, clinical and laboratory data that can be useful in predicting the short-term outcomes of patients with COVID-19. Such data could contribute to defining the phenotype of the COVID-19 inpatient who typically undergoes a worse short-term prognosis, helping clinicians to identify those patients who could need an early intensification of care.

Patients and Methods

This retrospective observational study was developed in the two hospitals of Ferrara's territory dedicated to COVID-19 inpatients: the "Arcispedale S. Anna" in Cona (Fe) and the "Ospedale del Delta" in Lagosanto (Fe). Between March 13 and June 13, 2020, 501 adult patients with the laboratory diagnosis of SARS-CoV-2 infection were consecutively hospitalized and enrolled; the diagnosis was confirmed with the reverse transcriptase-polymerase chain reaction (RT-PCR) test. We collected demographic, anamnestic and laboratory data that were later entered into an electronic report form and anonymized.

We reported the baseline symptoms and the vital signs, as well as the place where the infection occurred. Furthermore, we calculated their CCI (Charlson Comorbidity Score) for better stratification of their comorbidity status and the MEWS (Modified Early Warning Score) on admission to our medical departments, thinking of a possible role of this score in anticipating a possible worsening of the clinical condition[14]. Information about the items evaluated by the CCI and the MEWS can be found in the **Supplementary Table I** and **Supplementary Table II).** Inflammation was assessed by using the WBC (white blood cells) count, CRP (C reactive protein), procalcitonin and ferritin levels; the organ damage was evaluated through laboratory markers such as creatinine, BNP (brain natriuretic peptide), ALT (alanine transferase), isoamylase, CPK (creatine phosphokinase) and HS TnI (high sensitivity Troponin I). The only exclu-

sion criteria were age (patients younger than 18 years were excluded) and the negativity of the nasopharyngeal swabs to viral detection.

We evaluated the differences between patients in terms of COVID-19-related outcomes (IoC, intensification of care, meant as the need for non-invasive mechanical ventilation or for endotracheal intubation, and the in-hospital death). Patients needing IoC are recognized by the acronym "IoCp" while, for those who did not undergo IoC, we chose the acronym "nIoCp". The group of patients who survived and died during the stay are recognized with the acronym "iHDp" (in-hospital deceased patients) and "iHSp" (in-hospital survived patients), respectively.

The goal of the study was to identify the main predictors of IoC and in-hospital death, in order to build the "sketch" of the patient who undergoes more frequently worse COVID-19 outcomes.

For the compilation of this manuscript, we followed STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for reporting observational studies.

Statistical Analysis

Data analyses were performed by using SPSS 26.0 (IBM SPSS Statistics, IBM Corporation, Armonk, NY, USA) software.

The normal distribution of the continuous variables was analysed by using Kolmogorov-Smirnov and Shapiro-Wilk tests. Categorical variables were summarized by using frequencies and percentages, and continuous data were presented as mean± standard deviation (SD) when normally distributed or as median (InterQuartile Range in brackets) when not normally distributed. The Mann-Whitney U test was used for continuous variables and the χ^2 test was used for categorical variables. Variables with a p-value <0.05 in the univariate analyses were entered into multivariate logistic regression analysis. These logistic regression analyses were also performed for the variables that were previously found to independently predict the outcomes chosen, in order to establish which of them was/were more strongly related to the outcomes themselves. All p-values <0.05 are considered statistically significant.

Results

Between March 13 and June 13, 501 patients were consecutively hospitalized with a laboratory diagnosis of SARS-CoV-2 infection in the two hospitals of Ferrara's territory dedicated to COVID-19 inpatients. We collected their demographic, anamnestic and laboratory data on admission; vital signs were also registered, allowing us to calculate their MEWS score, in order to evaluate their clinical stability after the first visit. The comorbidity status was then evaluated through the CCI index.

We decided to generate four different statistical models to establish which personal, anamnestic, clinical and laboratory parameters were associated with COVID-19 outcomes. Variables were later entered into a unique logistic regression analysis that allowed us to understand which of them was more accurately related to the need for intensification of care, and/or to in-hospital death.

Table I shows the general features of the population, divided into subgroups according to the disease outcomes chosen; the p-values were calculated for each subgroup. The group of patients who needed an intensification of treatment (IoCp), compared to those who did not undergo IoC, presented a prevalence of males (69.3% *vs.* 44.1%, $p<0.001$) and smokers (28.7% *vs.* 17.7%, $p=0.012$). IoCp differed from nIoCp also in terms of mean age (68±12 *vs.* 73±18 years, $p<0.001$), place of infection, (prevalence of infection in nursing homes in the nIoCp group, 20.1% *vs.*7.1%, $p=0.001$) and presenting symptoms, with a greater association of fever with respiratory symptoms in the IoCp group (59.5% *vs.* 40.2%, $p<0.001$); nIoCp subjects presented more often with gastrointestinal symptoms (52.1% *vs.* 39.5%, $p=0.015$). IoCp presented with higher respiratory rates (23±7 *vs.* 21±6 breaths per minute, $p<0.001$), a higher MEWS score (2.2±1.5 *vs.*1.7±1.1 points, $p=0.004$), a lower PaO_2/FiO_2 ratio (216±94 *vs.* 305±107, $p<0.001$) and higher serum CRP (4.2 *vs.* 3.9 mg/dl, $p<0.001$).

Substantial differences were also found in terms of organ damage: IoCp patients had higher serum levels of LDH (394 vs. 259 mg/dl, $p=0.002$), isoamylase (35 *vs.* 25 U/L, $p<0.001$), ALT (36 *vs.* 17 U/L, $p<0.001$), CPK (76 *vs.*70 U/L, $p=0.04$) and ferritin (518 *vs.* 299 ng/ml, $p=0.02$). White blood cells (WBC), lymphocytes, CRP, procalcitonin, LDH, BNP, D-Dimer, isoamylase, ALT, CPK, ferritin and troponin I did not have a normal distribution and data concerning their serum levels were reported as median and interquartile range (IQR).

Logistic regression analyses were performed to estimate the independent contribution of each variable in determining the IoC.

Table I. Baseline and clinical characteristics of patients stratified by COVID-19 outcomes.

Personal informations	All patients (N=501)	IoCp (N=127)	NIoCp (N=374)	*p*	iHDp (N=126)	iHSp (N=375)	*p*
Age, years±SD	72±17	68±12	73±18	<0.001	82±10	68±17	<0.001
Males, n (%)	253 (50.5)	88 (69.3)	165 (44.1)	<0.001	62 (49.2)	191 (50.9)	0.57
Females, n (%)	248 (49.5)	39 (30.7)	209 (55.9)		64 (50.8)	184 (49.1)	
Smoke habit, n (%)	89 (17.8)	33 (28.7)	56 (17.7)	0.012	18 (18.8)	71 (18.9)	0.61
Place of infection							
Home	328 (65.4)	106 (83.5)	217 (58.0)	<0.001	62 (49.2)	261 (69.6)	<0.001
Nursing home	84 (16.8)	9 (7.1)	75 (20.1)	0.001	36 (28.6)	48 (12.8)	<0.001
Hospital	89 (17.8)	10 (7.9)	81 (21.7)	<0.001	25 (19.8)	66 (17.6)	0.57
Comorbidities							
Charlson Comorbidity Index, points±SD	2.0±2.3	1.7±2.4	2.1±2	0.005	3.1±2.3	1.7±2.2	<0.001
Diabetes	109 (21.8)	28 (22.0)	81 (21.7)	0.92	38 (30.2)	71 (18.9)	0.008
Hypertension	309 (61.7)	80 (64.5)	229 (61.7)	0.58	93 (75.6)	216 (58.1)	<0.001
Ischemic heart disease	63 (12.6)	15 (12.1)	48 (12.9)	0.80	26 (21.1)	37 (9.9)	0.001
Heart failure	56 (11.2)	11 (8.9)	45 (12.1)	0.32	26 (21.1)	30 (8.1)	<0.001
Chronic kidney disease (moderate or severe)	65 (13.0)	14 (11.2)	51 (13.9)	0.45	29 (23.6)	36 (9.7)	<0.001
Stroke or TIA	68 (13.6)	7 (5.6)	61 (16.5)	0.002	31 (25.4)	37 (9.9)	<0.001
PCOA	28 (5.6)	7 (5.6)	21 (5.7)	0.98	10 (8.3)	18 (4.8)	0.16
COPD	45 (9.0)	10 (8.1)	35 (9.5)	0.64	16 (13.1)	29 (7.8)	0.08
Cancer	85 (17.0)	15 (12.1)	70 (18.9)	0.08	34 (27.6)	51 (13.7)	<0.001
Metastatic cancer	27 (5.4)	7 (5.6)	20 (5.4)	0.91	8 (6.5)	19 (5.1)	0.55
Symptoms on admission							
Fever only	110 (22)	21 (17.2)	89 (23.9)	0.12	21 (17.4)	89 (23.8)	0.14
Respiratory only	136 (27.1)	28 (23)	108 (29)	0.20	45 (37.2)	91 (24.3)	0.006
Fever and respiratory	222 (44.3)	72 (59.5)	150 (40.2)	<0.001	53 (44.2)	169 (45.2)	0.84
Gastrointestinal only	244 (48.7)	49 (39.5)	195 (52.1)	0.015	63 (51.2)	181 (48.3)	0.57
Vital signs on admission							
Sistolic Blood Pressure, mmHg±SD	129±21	129±22	129±21	0.87	124±24	131±19	<0.001
Diastolic Blood Pressure, mmHg±SD	74±12	71±12	74±12	0.04	70±14	75±11	0.001
Heart Rate, bpm±SD	86±17	86±17	85±17	0.74	89±18	84±16	0.02
Respiratory Rate, bpm±SD	22±7	23±7	21±6	<0.001	24±7	21±6	<0.001
MEWS, points±SD	1.8±1.2	2.2±1.5	1.7±1.1	0.004	2.3±1.5	1.6±1.0	<0.001
PaO2/FiO2 ratio, n±SD	284±111	216±94	305±107	<0.001	236±98	299±111	<0.001
Laboratory markers on admission							
WBC, n/mm^3	6265 (5025-9598)	6390 (5480-10875)	6140 (4730-9353)	0.72	9050 (6000-11750)	6040 (4740-8965)	0.81
Lymphocytes, n/mm^3	960 (700-1455)	660 (660-1110)	1050 (720-1568)	0.08	900 (670-1390)	990 (728-1470)	0.22
CRP, mg/dl	3.9 (2.0-11.9)	4.2 (3.8-17.1)	3.9 (1.5-9.9)	<0.001	7.6 (6.1-15.7)	2.3 (1.5-10.0)	0.17
Procalcitonin, ng/ml	0.2 (0.1-0.7)	0.2 (0.2-1.1)	0.2 (0.05-0.5)	0.08	0.6 (0.2-1.6)	0.2 (0.05-0.4)	0.72
eGFR, ml/min	72.3 (44.4-90.6)	64.9 (50.6-92.0)	72.6 (41.7-89.9)	0.29	68.8 (23.5-71.9)	74.3 (54.4-95.1)	<0.001
LDH, mg/dl	277 (201-368)	394 (265-453)	259 (193-334)	0.002	294 (232-415)	273 (193-350)	0.001
BNP, pg/ml	77 (42-253)	80 (44-230)	74 (41-275)	0.79	230 (94-416)	62 (33-167)	<0.001
D-Dimer, ng/ml	1.0 (0.5-2.3)	1.2 (0.7-2.3)	0.8 (0.5-2.1)	0.12	1.2 (0.8-2.6)	0.9 (0.5-2.0)	0.58
Isoamylase, U/L	29 (21-52)	35 (21-69)	25 (21-49)	<0.001	36 (20-47)	25 (21-53)	0.08
ALT, U/L	22 (14-37)	36 (17-43)	17 (13-34)	<0.001	18 (13-37)	24 (14-36)	0.69
CPK, U/L	71 (46-183)	76 (54-287)	70 (41-154)	0.04	76 (46-353)	70 (46-167)	0.59
Ferritin, ng/ml	344(120-713)	518 (293-1348)	299 (104-625)	0.02	304 (270-1196)	421 (96-632)	0.39
Troponin I, ng/ml	17 (5-44)	19 (8-68)	16 (5-34)	0.86	41 (18-92)	13 (4-23)	0.80

Data are reported as number of participants (percentage) unless otherwise specified. IoCp, Patients who underwent intensification of care; nIoCp, Patients who did not undergo intensification of care; iHDp, In-hospital deceased patients; iHSp, In-hospital survived patients; TIA, Transient ischemic attack; PCOA, Peripheral chronical obstructive arteriopathy; Cancer, Localized or haematological cancer; WBC, White Blood Cells; CRP, C reactive Protein; eGFR, estimated Glomerular Filtration Rate; LDH, Lactate Dehydrogenase; BNP, Brain Natriuretic Peptide; ALT, Alanine aminotransferase; CPK, Creatine Phosphokinase. WBC, Lymphocites, CRP, Procalcitonin, LDH, BNP, D-Dimer, Isoamylase, ALT, CPK, Ferritin and Troponin I were not normally distributed and data concerning their serum levels are reported as median (IQR).

Table II. Logistic regression modelling for identifying the personal variables associated with outcomes.

Variables	OR	95% CI	*p*-value
Dependent variable: Intensification of Care			
Age	1.00	0.99-1.02	0.79
Sex (Male)	2.57	1.65-4.01	<0.001
Smoking habit	1.69	1.01-2.83	0.05
Home-acquired infection	1.55	0.27-8.85	0.62
Health care associated infection	5.54	0.86-35.63	0.72
Hospital-acquired infection	4.45	0.73-27.15	0.11
Dependent variable: In-hospital Death			
Age	1.08	1.06-1.11	<0.001
Sex (Male)	0.70	0.42-1.17	0.18
Smoking habit	1.03	0.55-1.95	0.93
Home-acquired infection	1.01	0.53-1.93	0.98
Health care associated infection	1.27	0.59-2.70	0.54

OR, Odds Ratio; CI, Confidence Intervals

The logistic regression models concerning the anamnestic data of patients and the place of infection are shown in Table II, while Table III shows the logistic regression analyses evaluating the anamnestic data. Table IV summarizes the analyses of the vital parameters registered on admission, together with the PaO_2/FiO_2 ratio, while in Table V we considered those laboratory data that were found to be substantially different between groups in the univariate analyses.

Analyses showed how sex (OR 2.57, 95% CI 1.65-4.01, $p<0.001$), the smoking habit (OR 1.69, 95% CI 1.01-2.83, $p=0.05$) and higher LDH values (OR 1.01, 95% CI 1.00-1.01, $p=0.008$) on ad-

Table III. Logistic regression modelling for identifying the variables concerning the clinical history of patients associated with outcomes.

Variables	OR	95% CI	*p*-value
Dependent variable: Intensification of Care			
Diabetes	1.52	0.79-2.92	0.22
Hypertension	1.40	0.89-2.20	0.15
Ischemic Heart Disease	1.41	0.64-3.11	0.39
Heart failure	1.19	0.49-2.85	0.70
Chronic Kidney Disease (III-IV-V stage)	1.09	0.40-2.99	0.87
Stroke or TIA	0.35	0.15-0.82	0.02
Localized or Hematological cancer	1.07	0.44-2.62	0.88
Metastatic cancer	3.60	0.51-25.7	0.20
CCI	0.80	0.60-1.08	0.14
Dependent variable: In-hospital Death			
Diabetes	0.80	0.41-1.55	0.51
Hypertension	1.32	0.69-2.54	0.40
Ischemic Heart Disease	0.67	0.30-1.51	0.33
Heart failure	0.70	0.27-1.81	0.46
Chronic Kidney Disease (III-IV-V stage)	0.62	0.28-1.35	0.23
Stroke or TIA	0.55	0.26-1.17	0.12
Localized or Hematological cancer	0.75	0.39-1.46	0.40
Metastatic cancer	0.79	0.26-2.41	0.68
CCI	1.17	1.06-1.28	0.001

OR, Odds Ratio; CI, Confidence Intervals; TIA, Transient Ischemic Attack; CCI, Charlson Comorbidity Index.

Table IV. Logistic regression modelling for identifying the clinical parameters, registered on admission, associated with outcomes.

Variables	OR	95% CI	*p*-value
Variables			
Presentation with fever and respiratory symptoms	1.67	0.79-3.52	0.18
Heart Rate	1.00	0.97-1.02	0.76
Systolic Blood Pressure	1.00	0.98-1.03	0.77
Diastolic Blood Pressure	0.98	0.94-1.02	0.37
Respiratory Rate	0.84	0.38-1.84	0.67
MEWS score	0.93	0.67-1.30	0.67
PaO_2/FiO_2 ratio	0.99	0.99-1.00	<0.001
Dependent variable: In-hospital Death			
Fever and respiratory symptoms at debut	0.82	0.43-1.59	0.56
Heart Rate	1.00	0.97-1.02	0.65
Sistolic Blood Pressure	0.98	0.96-1.00	0.08
Diastolic Blood Pressure	1.00	0.97-1.04	0.87
Respiratory Rate	2.17	1.11-4.26	0.02
MEWS score	1.53	1.11-2.12	0.009
PaO_2/FiO_2 ratio	0.99	0.99-1.00	0.03

OR, Odds Ratio; CI, Confidence Intervals. MEWS, Modified Early Warning Score.

mission were independently associated with the need for IoC. The same occurred for the history of stroke/TIA (OR 0.35, 95% CI 0.15-0.82, p=0.02) and for the PaO_2/FiO_2 ratio (OR 0.99, 95% CI 0.99-1.00, p<0.001).

The second outcome chosen was the in-hospital death: the iHDp population was older than iHSp's one (82±10 *vs.* 68±17 years, p<0.001), with a higher percentage of patients who contracted the infection in nursing homes (28.6% *vs.* 12.8%, p<0.001). The iHDp population had higher CCI scores (3.1±2.3 *vs.* 1.7±2.2 points, p<0.001), and showed a prevalence of subjects with diabetes (30.2% *vs.* 18.9%, p=0.008), hypertension (75.6% *vs.* 58.1%, p<0.001), chronic ischemic heart disease (21.1% *vs.* 9.9%, p<0.001), chronic heart failure (21.1% *vs.* 8.1%, p<0.001) and chronic kidney disease (23.6% *vs.* 9.7%, p<0.001) compared to the iHSp population. Patients of the iHDp group presented more often with respiratory symptoms (37.2% *vs.* 24.3%, p=0.006), lower values of systolic and diastolic arterial blood pressure (124±24 *vs.* 131±19 mmHg, p<0.001 and 70±14 *vs.* 75±11 mmHg, p=0.001, respectively), higher heart rates (89±18 *vs.* 84±16 beats per minute, p=0.02), respiratory rates (24±7 *vs.* 21±6 breaths per minute, p<0.001) and MEWS

Table V. Logistic regression modelling for identifying the laboratory parameters associated with outcomes.

Variables	OR	95% CI	*p*-value
Dependent variable: Intensification of Care			
CRP (mg/dl)	1.03	0.94-1.13	0.51
LDH (U/L)	1.01	1.00-1.01	0.008
Isoamylase (U/L)	1.01	0.99-1.02	0.45
ALT (U/L)	1.00	0.99-1.04	0.30
CPK (U/L)	1.00	1.00-1.00	0.25
Ferritin (ng/ml)	1.00	1.00-1.00	0.47
Dependent variable: In-hospital Death			
eGFR (ml/min)	0.98	0.97-0.99	0.001
LDH (U/L)	1.00	1.00-1.00	0.14
BNP (pg/ml)	1.00	1.00-1.01	0.006

OR, Odds Ratio; CI, Confidence Intervals; CRP, C Reactive Protein; LDH, lactic dehydrogenase; ALT, Alanine Transferase; CPK, Creatine Phosphokinase; eGFR, estimated Glomerular Filtration Rate; BNP, Brain Natriuretic Peptide.

scores (2.3±1.5 *vs.* 1.6±1.0 points, $p<0.001$). The arterial blood samples performed on admission showed that iHDp had a lower PaO_2/FiO_2 ratio (236±98 *vs.* 299±111, $p<0.001$), while the laboratory data, also collected on admission, showed that the subjects of the iHDp group had a lower eGFR (68.8 *vs.* 74.3 ml/min, $p<0.001$), higher serum LDH (294 *vs.* 273 mg/dl, $p=0.001$) and serum BNP (230 *vs.* 62 pg/ml, $p<0.001$).

Logistic regression analyses showed that age was independently associated with the in-hospital death (OR 1.08, 95% CI 1.06-1.11; $p<0.001$), together with the CCI (OR 1.17, 95% CI 1.06-1.28; $p=0.001$), the respiratory rate (OR 2.17, 95% CI 1.11-4.26; $p=0.02$), the MEWS score (OR 1.53, 95% CI 1.11-2.12; $p=0.009$) and the PaO_2/FiO_2 ratio (OR 0.99, 95% CI 0.99-1.00; $p=0.03$). Among laboratory markers, we found eGFR (OR=0.98, 95% CI 0.97-0.99; $p=0.001$) and serum BNP (OR=1.00, 95% CI 1.00-1.01; $p=0.006$) to be associated with the in-hospital death.

Finally, we performed a logistic regression analysis that evaluated all those variables previously resulted to be independently associated with the outcomes chosen; this was aimed at determining which variable had the strongest predictive role towards intensification of care and/or in-hospital death (Table VI).

As for the IoC, the strongest predictive variable was the PaO_2/FiO_2 ratio (OR 0.99, 95% CI 0.98-0.99, $p<0.001$,), followed by serum LDH (OR 1.01, 95% CI 1.00-1.01, $p=0.002$,) and male sex (OR 2.11, 95% CI 1.00-4.44, $p=0.05$). The variable that most effectively predicted the in-hospital death was age (OR 1.08, 95% CI 1.01-1.15, $p=0.02$) followed by the PaO_2/FiO_2 ratio (OR 0.99, 95% CI 0.99-1.00, $p=0.04$).

Discussion

In this study, we evaluated the role of each clinical, anamnestic and laboratory parameter of the patients admitted to our COVID-19 hospitals in the territory of Ferrara between March and June 2020. Our work aimed at finding those personal, clinical and laboratory factors that can be useful in the approach to COVID-19 inpatients and could collaterally predict COVID-19 outcomes (such as the need for intensification of care and the in-hospital death).

Among personal characteristics, male sex is the main negative prognostic factor for the IoC: past studies showed that sex has a considerable effect on the outcome of many infections and was associated with underlying differences in the immune response to infection. It is to remember that the eligibility of patients to an intensification of care is dictated above all by the estimated probability by patients of overcoming the critical phase of the disease. In this respect, scoring systems may guide clinicians throughout the process of choice, even if

Table VI. Logistic regression modeling for identifying the strongest predictive variables associated with COVID-19 outcomes.

Variables	OR	95% CI	*p*-value
Dependent variable: Intensification of Care			
Age	0.99	0.97-1.01	0.26
Sex (Male)	2.11	1.00-4.44	0.05
Smoking habit	1.33	0.57-3.13	0.51
Stroke or TIA	0.77	0.26-2.30	0.64
PaO_2/FiO_2 ratio on admission	0.99	0.98-0.99	<0.001
LDH (U/L)	1.01	1.00-1.01	0.002
Dependent variable: In-hospital Death			
Age	1.08	1.01-1.15	0.02
CCI	1.14	0.89-1.47	0.31
Respiratory Rate	1.05	0.93-1.18	0.45
PaO_2/FiO_2 ratio on admission	0.99	0.99-1.00	0.04
MEWS score	1.46	0.68-3.16	0.34
eGFR (ml/min)	0.99	0.96-1.10	0.23
BNP (pg/ml)	1.00	1.00-1.00	0.17

OR, Odds Ratio; CI, Confidence Intervals; TIA, Transient Ischemic Attack; LDH, Lactic dehydrogenase; CCI, Charlson Comorbidity Index; MEWS, Modified Early Warning Score; eGFR, estimated Glomerular Filtration Rate; BNP, Brain Natriuretic Peptide.

the clinical judgment remains the core skill when dealing with end-of-life events and decisions[15]. At the basis of the clinical judgment, the key role is played by unchangeable factors that independently modify the prognosis of patients, such as age, sex or comorbidities. Among these, age is certainly the first factor to be taken into consideration when evaluating the eligibility of patients towards the intensification of care, and it is no coincidence that the subjects who did not undergo IoC in our cohort of patients were on average older.

Aging itself is a prominent risk factor for both the severe disease and death by COVID-19. Already the first data from Chinese hospitals demonstrated that the case fatality ratio (CFR) of COVID-19 increased with age, ranging from 0.4% of patients who were 40 years old or younger to 14.8% of patients older than 80 years[16,17]. These data were confirmed in other countries later affected by the pandemic, with even higher CFRs registered in Europe[18,19] and in the U.S[20] concerning aged patients.

Age-related immune system remodelling, or immunosenescence, is considered the major reason for increased susceptibility to infection, and the age-related deficient response to virus by *de novo* T-cells seems to be the immuno-pathologic base of the higher vulnerability in older adults. This was postulated already in studies concerning influenza vaccinations[21], and age-differences in the responses to vaccinations were also reported in the cohort of COVID-19 inpatients of our territory[22].

Beyond the concept of "aging", that typically involves all biological systems, there is the effect of those diseases that usually correlate with age, such as strokes and TIAs, neoplastic diseases and diabetes, all conditions that characterize the subjects who did not need IoC in our population (nIoCp). The presence of chronic diseases, especially in aged patients, is among the criteria for excluding patients from invasive rescue techniques[23]. Another negative predictor for IoC among our patients was the smoking habit (OR 1.69): many studies have already investigated the role of smoke in patients with COVID-19, and a meta-analysis on 19 peer-reviewed papers with a total of 11,590 inpatients considered, showed that smoking can be classified as an independent risk-factor for severe COVID-19[24].

Multivariate logistic regressions allowed us to identify the independent role that serum LDH has towards IoC. LDH is an enzyme widely distributed in the body and strongly involved in the metabolism of carbohydrates; high enzymatic activities are found in heart, liver, skeletal muscles, kidneys and erythrocytes, while smaller amounts can be found in lungs, smooth muscle and brain. Due to its widespread activities in numerous tissues of the body, LDH is elevated in a variety of disorders causing cell degradation. Although the increase in total serum LDH activity is rather nonspecific, Drent et al[25], already in 1996, showed that acute lung injury with massive cell death is associated with a significant increase in LDH and, in particular, in its plasmatic isoenzyme *LDH 3*. This isoenzyme can be thus considered a useful biochemical index of lung injury mediated by acute immunological antibodies, with potential diagnostic and prognostic value in lung disease. In a recent Chinese study, serum LDH was validated as a marker for assessing clinical severity and for monitoring the treatment response in COVID-19 pneumonia. On this occasion, it was described how both the increase or decrease in LDH were indicative of radiographic progress or improvement, respectively[26]. LDH appears to be a good laboratory predictor of the need for IoC also in our study, and this indirectly reflects a condition of more extensive organ damage.

A significant protective role was played, instead, by a higher PaO_2/FiO_2 ratio. The role of PaO_2/FiO_2 ratio deserves some attention: this value, critically involved in evaluating the respiratory reserve and in defining the degrees of severity of the Acute Respiratory Distress Syndrome (ARDS), is strongly associated with COVID-19 because of the lung acute injury caused by SARS-CoV-2 and it needs to be calculated several times during the patient's stay to foresee a possible worsening of the clinical picture[27]. As expected, the patients who had a higher PaO_2/FiO_2 ratio on admission to hospital needed intensification of care less often than those subjects who presented with worse respiratory performances.

A quick analysis of the groups evaluating the in-hospital death allowed us to see how the patients who died during the hospital stay (iHDp) were on average older than survivors, with a higher CCI score (3.1±2.3 *vs.* 1.7±2.2 points) and prevalence of diabetes and chronic cardiovascular diseases among comorbidities. The current literature agrees with the important role played by such diseases in increasing the risk of severe COVID-19[28], as well as this happens in diabetic subjects[29].

Differences between groups are evident also in terms of vital signs, with higher respiratory and heart rates registered in the iHDp group: this reflects the different clinical conditions on admis-

sion of those patients who survive hospitalization compared to those who die within the short-term period of the stay. Regression analyses showed the predictive role of older ages and higher CCI scores towards worse short-term prognosis, as well as it happened for higher MEWS scores and higher respiratory rates registered on admission. A protective role was played by the PaO_2/FiO_2 ratio, similarly to what was observed in the regression analyses concerning the intensification of care; the role of PaO_2/FiO_2 ratio was already discussed above.

Explaining why an older age and a greater CCI score are strongly associated with the in-hospital death is quite easy and it is strictly linked to the concept of aging, as already explained. To "weigh" the clinical history of each inpatient, we used the CCI, based on the international classification of illnesses: this was originally intended to predict the 10-year survival of patients with multiple comorbidities, while to date it has an important significance for better evaluating the aggressiveness of the medical treatments to which a patient must be subjected, based on his life expectancy. Already an English study on geriatric patients showed that the presence of comorbidities is an independent risk factor for hospitalization and death by COVID-19 while different studies showed that the CCI score can be predictive of poor prognosis also in the case of SARS-CoV-2 infection[30,31]. The items considered by the CCI score should be carefully evaluated because of their ability to predict an extremely unfavorable outcome, even for patients in a short-term period (such as the hospitalization period).

Once all regression analyses were performed, we decided to consider again all the variables found to be independently associated with the three COVID-19 outcomes chosen, to build the "sketch" of the COVID-19 inpatients who are more likely to have a poor prognosis.

The last regression analysis allowed us to understand that the patient who typically undergoes an intensification of care is male, with a low PaO_2/FiO_2 ratio and high serum LDH on admission.

The PaO_2/FiO_2 ratio resulted to be sufficiently useful in predicting also the in-hospital mortality, but age was even more reliable in determining the prognosis of these patients within the hospitalization period, showing how the patients at higher risk of in-hospital mortality were elderly and with lower respiratory performances, already on hospital admission. The role of age towards a worse prognosis in patients with COVID-19 was already discussed and it is coherent with the findings of other studies like this.

Our study has several limitations, particularly related to its retrospective nature and the limited size of sample did not allow us to prevent confounding factors or selection biases. Moreover, the retrospective analysis of data did not allow us to modify our behaviour towards COVID-19 inpatients during the period of observation. However, we believe that studies like this can be useful for the early identification of the patients with a higher risk of needing IoC or of having a worse prognosis. This could help increase the attention of the clinicians, already at the time of admission to the wards, and modify their approach towards those patients who can have a worsening of their clinical conditions during hospitalization.

Conclusions

Male sex, high serum LDH, and a low PaO_2/FiO_2 ratio can be considered independent prognostic factors for the intensification of care.

Aged patients who present with a low PaO_2/FiO_2 ratio and, thus, with worse respiratory performances, undergo more often than other patients a poor outcome within the hospitalization period.

Providing the sketch of these subjects could be useful for clinicians to be prepared in case of early worsening in the clinical conditions and to choose the right treatment, to avoid a worse outcome in COVID-19 inpatients.

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Statement of Ethics

We followed STROBE guidelines (Strengthening the Reporting of Observational Studies in Epidemiology) for reporting observational studies as for the compilation of this manuscript. All patients signed an informed consent when possible, in case the patient was unable to sign, the consent was given by his/her next of kin. The local Ethics Committee "Comitato Etico Indipendente di Area Vasta Emilia Centro (CE-AVEC)" approved the protocol of this study; the protocol code is 712/2020/Oss/AOUFe.

Conflict of Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Authors' Contributions

SG, BB and AB acquisition, analysis, interpretation of data and drafting the article. NF, CR, MEB, LM, SG, MG, MF, FDU and ER acquisition and analysis of data. CVF, SP and GNC the conception and design of the study, revising it critically for important intellectual content and final approval of the version to be submitted. AP the conception and design of the study, drafting the article and revising it critically for important intellectual content and final approval of the version to be submitted.

ORCID ID

Angelina Passaro: 0000-0001-8462-7000.

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