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Italian SARS-CoV-2 patients in intensive care: towards an identikit for subjects at risk?

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Abstract. – OBJECTIVE: To investigate patient characteristics and factors that increase the risk of being admitted to intensive care and that influence survival in cases of SARS-CoV-2 pneumonia.

PATIENTS AND METHODS: One-hundred and ninety-one SARS-CoV-2 patients were admitted to the "Fondazione Poliambulanza di Brescia" Hospital (Brescia, Lombardy, Italy) in the period 1st March 2020 to 11th April 2020. Data on demographics, clinical presentation at admission, co-morbidities, pharmacological treatment, admission to intensive care and death was recorded. Logistic regression and survival analysis were carried out to investigate the risk of being admitted to intensive care and the risk of death.

RESULTS: The mean age of the study cohort was 64.6±9.9 years (range 20-88). Median BMI was 28.5±5 kg/m². Fever (81%) and dyspnea (65%) were the most common symptoms on admission. Most of patients (63%) had at least one co-existing disease. The 157 (82%) patients admitted to intensive care were more likely to be of intermediate age (60-69 years; OR 3.23, 95% CI 1.32-8.38), overweight (OR 2.66, 95% CI 1.02-7.07) or obese (OR 5.63, 95% CI 1.73-21.09) and with lymphocytopenia (OR 2.75, 95% CI 1.17-6.89) than the 34 patients admitted to the ordinary ward. During intensive care, 50% of patients died and their death was associated with older age (HR 2.06, 95% CI 1.07-3.97), obesity (HR 2.23, 95% CI 1.15-4.35) and male gender (HR 1.9, 95% CI 1.02-3.57).

CONCLUSIONS: We found that admission to intensive care and poor survival were associated with advanced age and higher body mass index, albeit with differences in statistical significance. Pre-existing diseases and symptoms on admission were not associated with different clinical outcomes. Interestingly, male gender was more prevalent among SARS-CoV-2 patients and was related negatively to survival, but it was not associated with more frequent admission to intensive care.

Key Words:
SARS-CoV-2, Intensive care, COVID-19.

Introduction

In early December 2019, the first cases of pneumonia of unknown origin were identified in Wuhan, China[1]. The new lipid-enveloped RNA virus was named *severe acute respiratory syndrome coronavirus 2* (SARS-CoV-2) because its symptoms were similar to those of SARS-CoV[2]. By 25th February 2020, more than 80,000 cases

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had been identified in China and on 11th March 2020, The World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) a public health emergency of international proportions[2,3].

In Italy, by 21st March 2020, a total of 53,578 cases of COVID-19 had been diagnosed by regional reference laboratories as positive for SARS-CoV-2, including 2857 in Intensive Care Units (ICU) and there had been 4825 deaths (official data from the Italian Ministry of Health, http://www.salute.gov.it/, and the Italian Department of Civil Protection, http://www.protezionecivile.gov.it/), Lombardy being the Italian region most affected. An enormous drawback of the pandemic was saturation of intensive care capacity. At the time, about 70% of IC beds in Italian hospitals were occupied by critical COVID-19 patients[4]. Since negative outcome involves intensive care, delineation of associated risk factors could enable early identification of patients with a poor prognosis. The European Center for Disease Prevention and Control (ECDC) reports that population groups susceptible to severe forms of disease requiring intensive care and with a higher mortality rate include people over 60 years of age, male, with concomitant conditions such as hypertension, diabetes, cardiovascular disease, chronic respiratory disease and cancer[5].

A study by Guan et al[3] on 1099 COVID-19-positive patients from 552 hospitals in 30 Chinese provinces showed that 173 severe symptomatic patients had the following comorbidities: hypertension (23.7%), diabetes (16.2%), coronary heart disease (5.8%) and cerebrovascular disease (2.3%).

Some retrospective and cohort studies conducted on Wuhan COVID-19-positive patients showed that hypertension, diabetes, cardiovascular disease and advanced age were among the risk factors that could lead to intensive care. Most of these cohort studies[6-8] showed a prevalence of male patients among those in whom the infection took a severe course.

Integrated surveillance of Italian COVID-19 patients by the Istituto Superiore di Sanità (ISS) updated to 22nd March 2020, indicates that the median age of COVID-19-positive patients who died (80.5 years) was more than 15 years older than the median age of all those who contracted the infection (63 years). The percentage of deceased over 60 years of age accounted for more than 10% of the total number of deaths from COVID-19. Among the deceased, at least one comorbidity was reported in 88% of cases. The major comorbidities identified in China were the same as in 3200 Italian deceased (updated to 20th March 2020) reported by the said Institute: arterial hypertension (73.8%), ischemic heart disease (30.1%) and diabetes (33.9%)[9].

Here our aim was to describe the demographics and clinical characteristics of patients admitted to a hospital in the city of Brescia, Lombardy, the most severely affected region of Italy. Additionally, to identify the factors associated with admission to intensive care and survival.

Patients and Methods

A total of 191 (149 males and 42 females) patients testing positive for SARS-CoV-2 RNA were admitted to the "Fondazione Poliambulanza di Brescia" hospital (Brescia, Lombardy, Italy) in the period 1st March 2020 to 11th April 2020. They included 157 critically ill patients from the Intensive Care Unit (ICU) and 34 stable patients from the Medical and Surgical Departments (hereafter referred to as "controls"), who did not develop severe respiratory failure.

The following data was recorded: demographic data (age, gender), clinical characteristics on admission to hospital (Body Mass Index, body temperature, coughing or dyspnea), laboratory parameters on admission (blood leukocyte and lymphocyte counts, respiratory frequency (fR), peripheral oxygen saturation (SpO2), certain pre-existing co-morbidities (diabetes mellitus and cardiovascular disease) and therapy (cortisone, immunosuppressive, anti-inflammatory, anti-viral, chloroquine, tocilizumab). Clinical outcome (discharge, admission to IC, death) was also recorded. For IC patients, ICU entrance date and date of death were recorded.

BMI values were classified in three categories: optimal (<25 kg/m^2), overweight (25-30 kg/m^2) and obese (≥30 kg/m^2). Age was classified in tertiles: young (19-60.9 years), intermediate (60.9-68.9 years) and elderly (68.9-88 years). Blood lymphocyte count was classified as lymphocytopenia for values under 0.8 10^9/L. SpO2 and fR were classified as high and low for thresholds of 90% and 24 min, respectively.

Statistical Analysis

To investigate the risk of admission to intensive care, we estimated a logistic regression and then assessed model prediction by leave-one-out cross-validation. On the ICU subset, we assessed Kaplan Meier survival curves, testing for differences between survival curves with the Mantel-Haenszel test. We then fitted a Cox Proportional Hazard model, adjusting for BMI (3 levels), age (3 levels), sex, temperature and lymphocyte count. We assessed the proportional hazard assumption by visual inspection of the residuals and by global testing. We performed an additional logistic regression to analyze the overall risk of death for the whole sample.

Continuous data is reported as medians and interquartile ranges (IQR). Comparisons were conducted by *t*-test and χ^2-test, for continuous and categorical data, respectively. Descriptive statistics are provided for all the analyses. Results are expressed as odds ratio (OR), hazard ratio (HR) and 95% confidence intervals (CI) for the logistic and Cox regressions, respectively. All the analyses were run with R software.

The present study is a retrospective case series and did not require the approval of an Ethics Committee.

Results

Factors Predicting ICU Admission

All 191 patients considered in this study tested positive to a SARS-CoV-2 RNA swab-test. Table I shows descriptive statistics for the 191 patients divided into ICU and Control groups. The sample was 78% male and patients had a mean age of 64.5±9.9 years. Fever (81.15%) and dyspnea (64.92%) were the most common symptoms on admission.

No significant difference in age or BMI (Student *t*-test) or in sex, age class or BMI (χ^2) was found between ICU and control patients. On the other hand, SpO_2 and leukocyte count were lower in control than in ICU patients (Table I).

To identify risk factors for admission to IC, we challenged several logistic regression models looking for the one with the highest accuracy and predictability and the lowest Akaike Information Criterion (a parameter of model fit). The best logistic regression model included BMI classes, age classes and presence of cardiovascular disease. The fitted values of coefficients are shown in Table II. Relevant risk factors were elevated BMI (overweight OR = 2.66, 95% CI 1.02-7.07; obesity OR = 5.63, 95% CI 1.01-11.45), intermediate-age class (OR = 3.00, 95% CI 1.01-9.44), lymphocytopenia (OR = 2.75, 95% CI 1.17-6.89) and a slight increase in SpO2 (OR = 1.09, 95% CI 1.03-1.15).

The model showed an accuracy of 0.81 (95% CI 0.75-0.87) and a predictability of 78% by leave-one-out cross-validation (and the same results by 15-fold cross-validation). Using the predicted values from the model, we obtained a sensitivity of 97% and a specificity of 23%.

Survival Analysis for ICU Patients

Table III shows the descriptive statistics for ICU patients (n = 157). Seventy-eight (50%) died and median survival was 21 days after admission to IC. Among those who died, 33% were obese and 44% were in the (69-88)] age class, whereas those who survived were younger (mean age 61±10.04 years) and only 19% were obese.

Figure 1 shows the Kaplan-Meier survival curves and 95% confidence intervals. The curves for BMI (*p*-value = 0.03) and sex (*p*-value = 0.02) were significantly different, but not those for age (*p*-value = 0.089). The Cox model (Figure 2 and **Supplementary Table I** in SM) showed a higher risk of death for male (Hazard Risk, HR, = 1.9, 95% CI 1.02-1.79), obese (HR = 2.23, 95% CI 1.15-4.35) and high-age class patients, while cardiovascular disease were not statistically significant attributes. The test and visual inspection of residuals (data not shown) confirmed that the data supports a proportional hazard assumption (*p*-value = 0.98).

Finally, we estimated the odds ratio of dying using all the data collected (**Supplementary Tables II** and **III**). We confirmed that those who died were older and generally obese or overweight. We did not find any significant difference in clinical presentation or parameters between the two groups. The odds ratios confirmed that age and BMI could be regarded as risk factors, unlike lymphocyte count and peripheral oxygen saturation.

Discussion

Understanding the risk factors most predictive of needing intensive care in the new coronavirus pandemic could help clarify prognosis and provide indications for public health planning. Although older age, male gender and pre-existing chronic diseases emerged as risk factors[3,10], the identikit of COVID-19 patients requiring intensive care is still far from clear.

In our retrospective study, we observed a higher percentage of critically ill among older and male

Table I. Descriptive statistics for sample split by ICU patients and Controls (non ICU).

Demographic features		**ICU n = 157**	**Controls n = 34**	***p*-value**
Male/Female (%, male)		124/33 (78.98%)	25/9 (73.53%)	0.64
Age, median (IQR)		66 (59-70)	67 (59-75.75)	0.173
Age tertiles, n (%)	Low	44 (28.03%)	11 (32.35%)	0.289
	Intermediate	59 (37.58%)	8 (23.53%)	
	High	54 (34.39%)	15 (44.12%)	
BMI, median (IQR)		27.8 (25.7-31.1)	25.85 (23.77-29.07)	0.083
BMI classes, n (%)	Optimal	32 (20.38%)	13 (38.24%)	0.068
	Overweight	73 (46.5%)	14 (41.18%)	
	Obese	52 (32.12%)	7 (20.59%)	
Clinical presentation				
Body temperature, median (IQR)		38 (37.5-38.6)	38 (37.85-38.87)	0.287
Cough, yes/no (% yes)		68/89 (43.31%)	32/2 (94.12%)	< 0.001
Dyspnea, yes/no (% yes)		104/53 (66.24%)	20/14 (58.82%)	0.533
fR (BPM), median (IQR)		23.5 (18-39)	25 (20-30)	0.853
fR high/low, (% high)		64/72 (47.06%)	20/14 (58.82%)	0.300
SpO2 %, median (IQR)		94 (88-97)	90 (87.25-93.5)	0.036
SpO2 >90%, (% high)		66/91 (42.04%)	16/18 (47.06%)	0.73
Clinical parameters				
Leukocytes, median (IQR)		8.02 (5.34-11.15)	6.78 (5.01-9.18)	< 0.001
Lymphocytes, median (IQR)		0.79 (0.59-1.02)	1 (0.67-1.45)	0.281
Lymphocytes <0.8 109/L, (% low)		77/77 (50%)	11/23 (32.35%)	0.094
Comorbidities				
Diabetes mellitus, yes/no (% yes)		25/132 (15.92%)	9/25 (26.47%)	0.226
Cardiovascular disease., yes/no (% yes)		94/63 (59.87%)	20/14 (58.82%)	1.000
Therapies				
Cortisone, yes/no (% yes)		74/83 (47.13%)	10/24 (29.41%)	0.090
Immunosuppressive, yes/no (% yes)		6/151 (96.18%)	0/34(0%)	-
Anti-inflammatory, yes/no (% yes)		1/156 (0.64%)	0/34(0%)	-
Antiviral, yes/no (% yes)		83/74 (52.87%)	0/34(0%)	-
Chloroquine, yes/no (% yes)		74/83 (47.13%)	11/23 (32.35%)	0.167
Tocilizumab, yes/no (% yes)		5/152 (3.18%)	2/32 (5.88%)	0.798

Legend: BMI, body mass index; BPM, breaths per minute; fR, respiratory frequency; ICU, intensive care unit; IQR, interquartile range; n sample size; *p*-value, from t-test statistics; SpO2, peripheral oxygen saturation; tertiles: low (19,60.9], intermediate (60.9,68.9] and high (68.9,88]; classes: optimal < 24.9, overweight [25-29.9) and obese > 30. *t*-test *p*-value for continuous variables and Chi-square for categorical variables.

Table II. Regression model to predict risk factors leading to intensive care.

	Odds ratio (OR)	**95% vonfidence intervals (CI)**
BMI - Optimal	Reference	-
BMI - Overweight	2.66	(1.02,7.07)
BMI - Obese	5.63	(1.73,21.09)
Age - Low	Reference	-
Age - Intermediate	3	(1.01,9.44)
Age - High	1	(0.35,2.87)
Lymphocytes <0.8	2.75	(1.17,6.89)
SpO2	1.09	(1.03,1.15)
Cardiovascular disease	1.2	(0.48,2.97)

patients than younger and female, confirming previous observations in other studies[3]. This imbalance in risk distribution has been ascribed to other concurring risk factors, such as smoking, which is more frequent in older males[3,11].

The risk of being admitted to intensive care and survival were both negatively influenced by higher BMI. One third of ICU patients were obese against 21% of the control group. Likewise, BMI was also observed to be higher in critically ill patients and in non-survivors than survivors in a Wuhan study, making it an important determining factor for outcome[12]. Similar associations

Table III. Descriptive statistics for the ICU patients split by deceased and not deceased.

Demographic features		Deceased N = 79	Not deceased N = 78	*p*-value
Male/Female (% male)		67/12 (84.81%)	57/21 (73.56%)	0.023
Age, median (IQR)		67 (62-71.75)	63 (56-68)	< 0.001
Age tertiles, n (%)	Low	14 (17.72%)	30 (38.46%)	0.07
	Intermediate	30(37.97%)	29 (37.18%)	
	High	35 (44.3%)	19 (24.36%)	
BMI, median (IQR)		28.3 (26.05-31.2)	27.7 (25.05-29.4)	0.068
BMI classes, n (%)	Optimal	13(16.46%)	19 (24.36%)	0.024
	Overweight	33 (41.77%)	40 (51.28%)	
	Obese	33 (41.77%)	19 (24.36%)	
Clinical presentation				
Body temperature, median (IQR)		38.1 (37.6-38.55)	38 (37.2-38.8)	0.2933
Cough, yes/no (% yes)		337/42 (48.84%)	31/47 (39.74%)	0.513
Dyspnea, yes/no (% yes)		55/24 (69.92%)	49/29(62.82%)	0.277
fR (BMP), median (IQR)		24 (20-30)	22.5 (18-30)	0.822
fR high/low, (% high)		34/36 (48.57%)	30/36 (45.45%)	0.568
SpO2 %, median (IQR)		93 (87-96)	95 (90-97)	0.115
SpO2 >90%, (% high)		22/44 (33.3%)	13/50 (20.63%)	0.361
Clinical parameters				
Leukocytes, median (IQR)		8.2 (5.67-10.8)	7.82 (5.29-11.4)	0.859
Lymphocytes, median (IQR)		0.78 (0.55-0.99)	0.8(0.59-1.08)	0.57
Lymphocytes <0.8 109/L, (% low)		40/37 (51.95%)	37/40 (48.05%)	0.857
Comorbidities				
Diabetes, yes/no (% yes)		14/65 (17.72%)	11/67 (14.1%)	0.362
Cardiovascular disease., yes/no (% yes)		51/28 (64.56%)	4/35 (55.13%)	0.275
Therapies				
Cortisone, yes/no (% yes)		40/39 (50.63%)	34/44 (43.59%)	0.497
Immunosuppressive, yes/no (% yes)		3/76 (3.8%)	3/75 (3.85%)	0.791
Anti-inflammatory, yes/no (% yes)		1/78 (1.29%)	0/78 (0%)	-
Antiviral, yes/no (% yes)		43/36 (54.43%)	40/38 (51.28%)	0.354
Chloroquine, yes/no (% yes)		38/41 (51.9%)	36/42 (46.15%)	0.73
Tocilizumab, yes/no (% yes)		2/68 (2.86%)	3/75 (3.85%)	0.864

Legend: BMI, body mass index; BPM, breaths per minute; fR, respiratory frequency; IQR, interquartile range; n sample size; p-value, from *t*-test statistics; SpO2, peripheral oxygen saturation; tertiles: low (19,60.9], intermediate (60.9,68.9] and high (68.9,88]; classes: optimal < 24.9, overweight [25-29.9) and obese > 30. *t*-test *p*-value for continuous variables and Mantel-Haenszel for categorical variables.

between higher BMI and risk of hospitalization have already been described for patients with other respiratory diseases, such as influenza virus, other coronavirus species, metapneumovirus, parainfluenza virus and rhinovirus[13]. The reason for this association could be related to respiratory mechanics, which put obese patients at particular disadvantage due to reduced residual functional capacity and static compliance. A secondary hypothesis could involve the altered lipid profile of obese patients. Disorders of lipid metabolism can alter membrane lipid rafts, which play a role in viral entry into the host cell. Lipids could therefore have a role in SARS-CoV-2 infection. The targeting of host lipids has consequently been considered a possible antiviral approach[14].

Another relevant factor that we found to be associated with severer disease was lymphocytopenia at admission. In our cohort, 46% of patients had lymphocytopenia and it was associated with higher risk of ICU admission (OR = 2.75, 95% C.I 1.17-6.89, Supplementary Table III). This data agrees with reduced lymphocyte count in 28-63% of COVID-19 patients across studies with a consis-

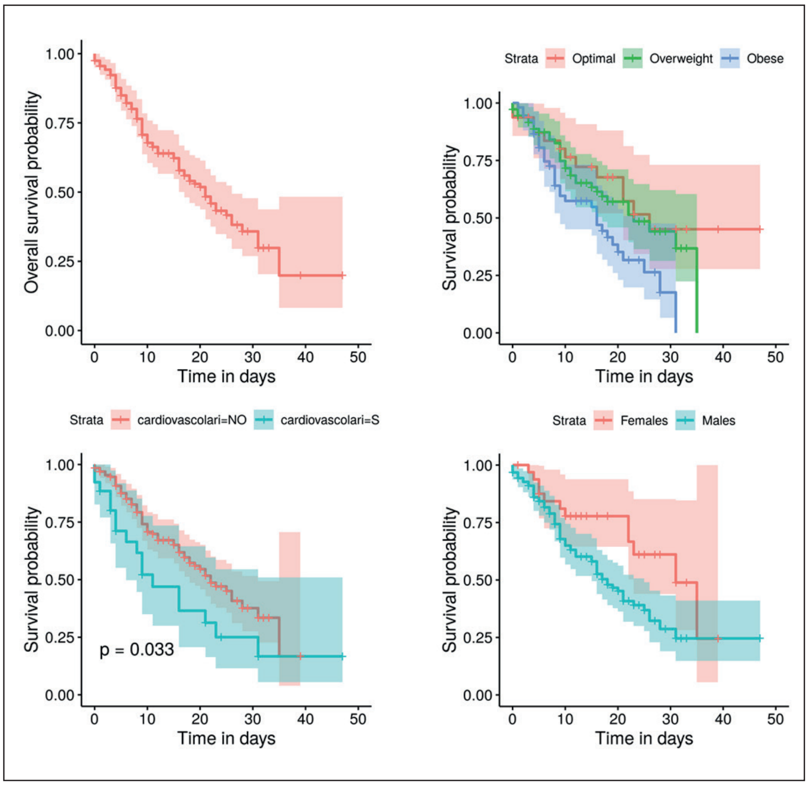

Figure 1. Kaplan-Meir survival curves. From top left: for all data, split by BMI class, Age class and Sex, the shadow area represents the 95% confidence intervals.

tent association with poor clinical outcomes[15]. Statistical analysis showed a slight increase in SpO2 in ICU patients, which was unexpected. However, this paradoxical observation may reflect differences in recording conditions for SpO2. Patients admitted to intensive care are urgently intubated with invasive ventilators and SpO2 is then recorded, while SpO2 was recorded in the control population while they were breathing autonomously.

This study has some limitations. The dataset is based on observational data collected at the peak of the pandemic from a single hospital over a short time period and the results may therefore not be representative of the general population. A source of bias in the data set could come from the fact that some of the clinical parameters were recorded under different conditions, such as on admission to the hospital or to intensive care, and for patients whose condition was severe, pre-existing factors were obtained by interview with family members.

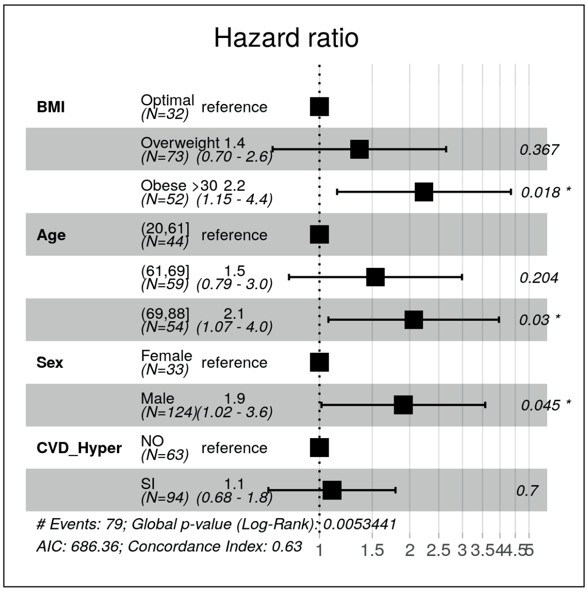

Figure 2. Forest plot of the Cox Model estimates, with Hazard ratio, 95% confidence intervals and *p*-values.

Conclusions

In summary, age and obesity were the strongest negative risk factors for severity and mortality. Another risk factor for severity was lymphocytopenia, reflecting the role of the immuno-inflammatory system in SARS-CoV-2 pneumonia.

Conflict of Interest

The authors declare that they have no commercial associations that might pose a conflict of interest in connection with the submitted article.

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