Journal of Immunology and Infectious Diseases
Volume 7 | Issue 1
ISSN: 2394-6512

Letter Open Access

Covid-19: Which Baseline Co-Factors are Associated with a Worse Prognosis?

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Citation: Scala E, Abeni D, Tedeschi A, Manzotti G, Yang B, et al. (2020) Covid-19: Which Baseline Co-Factors are Associated with a Worse Prognosis? J Immunol Infect Dis 7(1): 103

Received Date: December 05, 2020 **Accepted Date:** December 28, 2020 **Published Date:** December 30, 2020

Keywords: SARS-CoV-2; Covid-19; Allergy; Immune response

To the Editor

Critically ill Covid-19 patients are characterized by an uncontrolled cytokine storm that reflects a profoundly dysregulated immune response and represents probably the major factor contributing to mortality. Cytokines can lead to vascular leakage, activation of complement, and activation of the coagulation cascade, which in turn cause acute respiratory distress syndrome (ARDS), myocardial dysfunction, hypotension, and coagulopathy [1-3]. Male sex, older age, and current smoking, along with comorbidities such as pulmonary disease, hypertension, diabetes, coronary heart disease, and obesity have been variably associated with a poorer prognosis at an early stage of the disease [2,4]. However, the clinical consequences of SARS-CoV-2 infection are extremely variable ranging from a complete absence of symptoms (inapparent infection) to fatal ARDS with multiple organ dysfunction [5], The cytokine storm does not occur in less severe patients [1,6]. Thus, individual features beyond the viral load must play a role in determining the severity of the infection acting as risk factors.

We analyzed retrospectively 313 Italian adults (144 females, 46%) mean age 67±14 years (range 25 - 100 years), hospitalized for SARS-CoV-2 infection confirmed by the detection of viral nucleic acid in nasal and/or pharyngeal clinical specimens in Covid-19 centres sited in Lombardy, Lazio, and Aosta Valley. The doctors working in these centres recorded age, sex, and smoking habits of the patients along with several co-morbidities including obesity, diabetes, hypertension, coronary heart disease, and thrombosis, and graded globally the severity of respiratory disease. The disease was classified as mild, severe, or very severe based on no need for respiratory assistance, need for non-invasive respiratory assistance or need for invasive respiratory assistance or death, respectively. This latter subset was chosen as the outcome of interest. Patients' data were anonymized, and the Internal Review Board of the promoting centre approved the study.

The association between severity of COVID-19 and the clinical co-factors recorded was studied in univariate and multivariate analyses. Each variable of interest was dichotomized as negative or positive to study the proportion of subjects with a given clinical status. Categorical variables were analyzed using the Pearsons' χ^2, Fisher's exact test, with Yates's correction for continuity when indicated. Multiple logistic regression was performed to estimate the degree of association of the main exposure variables with COVID-19 severity after simultaneously adjusting for all the other variables of interest. P values <0.05 were considered significant.

The SPSS/PC+ statistical package for statistical evaluation (IBM SPSS Statistics for Windows, Version 26.0.0.1 - IBM Corp., Armonk, NY, USA) was used to analyze the data.

Pulmonary disease was mild or severe in 254 cases (81.2%) and very severe in 59 patients (18.8%%). The demographic and clinical features of the study population are summarized in Table 1.

Covid-19													
	Very severe					Mild / severe							
Variable	Level	N	%	N	%	N	%	ORc	95%CI	P-value	ORadj	95%CI	P-value
Overall		313	-	59	18.8%	254	81.2%						
Sex	Female	144	46.0%	19	13.2%	125	86.8%	1			1		
	Male	169	54.0%	40	23.7%	129	76.3%	2	1.1-3.8	0.013	1.9	0.99-3.6	0.055
Age group (years)	<65	125	39.9%	22	17.6%	103	82.4%	1			1		
	65-74	87	27.8%	12	13.8%	75	86.2%	0.8	0.3-1.6	0.229	0.6	0.3-1.5	0.298
	75+	101	32.3%	25	24.8%	76	75.2%	1.5	0.8-3	0.125	0.96	0.4-2.1	0.919
Smoking	No	153	48.9%	22	14.4%	131	85.6%	1					
	Yes	91	29.1%	23	25.3%	68	74.7%	2	1.04-3.9	0.026			
	Ex	69	22.0%	14	20.3%	55	79.7%	1.5	0.7-3.2	0.182			
Diabetes	No	259	82.7%	42	16.2%	217	83.8%	1			1		
	Yes	54	17.3%	17	31.5%	37	68.5%	2.4	1.2-4.6	0.008	1.9	0.95-3.9	0.068
Hypertension	No	119	38.0%	16	13.4%	103	86.6%	1					
	Yes	194	62.0%	43	22.2%	151	77.8%	1.8	0.98-3.5	0.39			
Coronaropathy	No	232	74.1%	33	14.2%	199	85.8%	1			1		
	Yes	81	25.9%	26	32.1%	55	67.9%	2.8	1.6-5.2	< 0.001	2.5	1.3-4.8	0.007
Thrombosis	No	274	87.5%	42	15.3%	232	84.7%	1			1		
	Yes	39	12.5%	17	43.6%	22	56.4%	4.2	2.1-8.7	< 0.001	3.1	1.4-6.7	0.005
Obesity	No	278	88.8%	47	16.9%	231	90.9%	1			1		
	Yes	35	11.2%	12	34.3%	23	9.1%	2.6	1.2-5.5	0.013	2.4	1.04-5.3	0.039

Table 1: Demographic and clinical features of the study population. Frequency of, crude OR, and adjusted OR from multiple logistic regression model for very severe COVID-19 patients

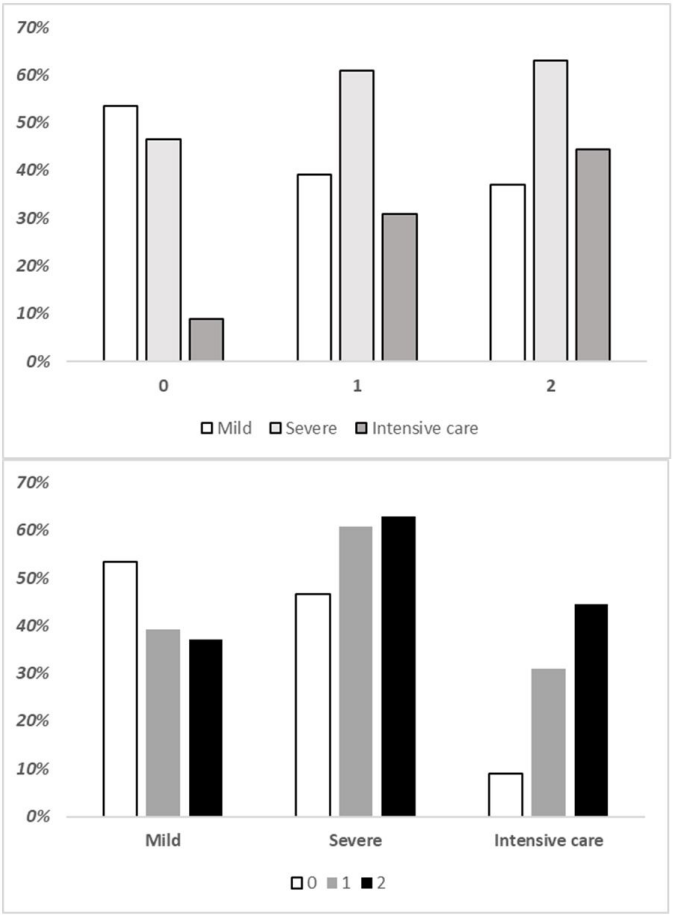

Figure 1: Analysis of Coronaropathy, thrombosis, and obesity co-factors as a function of COVID-19 severity **(A)** and comorbidities index **(B)**

In univariate analysis, male gender was significantly associated with admission to intensive care units (23,7% vs 13,2% in female, p = 0.013). Smokers had a significantly higher prevalence of intensive care admission than non-smokers (25.3% vs 14.4%, p=0.026) (Table 1). Coronaropathy (p = <0.001), thrombosis (p = <0.001), and obesity (p = 0.013) were all associated with a worse pulmonary COVID-19-related involvement. These comorbidities remained significant after simultaneous adjusting for all the other variables of interest (Right columns of Table 1 and Figure 1). By considering these comorbidities together we created an additional index which shows that the presence of any one of these factors shows an Orc = 4.5 and that 2 or more factors have an Orc = 8.0. These values remained statistically significant also after multiple adjustments for age, sex, and presence of diabetes (ORadj for 1 factor = 3.9, 95%CI 2.0 – 7.8, p <0.001; ORadj for 2 or 3 factors = 7.7, 95% CI 3.0 – 20.0, p <0.001).

Our results indicate that obesity, coronaropathy, and thrombosis are independent markers of risk of very severe COVID-19. The presence of any one of these comorbidities increase the risk of very severe disease from 9% to 31%, and when two of these factors are present the risk further increases to 44%.

In conclusion, clinicians should be particularly alert in the presence of these comorbidities, especially when at least two of obesity, coronaropathy, and thrombosis are present at the same time.

Conflict of Interest

No author has conflicts of interest to declare.

Authors Contributions

RA and ES conceived the study. RA coordinated the study and wrote the manuscript. AT, GM, BY, PB, AM, MG, AS, and FS cared for Covid-19 patients and provided the clinical data. DA performed the statistical analysis.

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