

# Predictive comorbidities of hospital admission in 1,571 SARS-CoV-2 positive patients: analysis of administrative data from an Italian Local Health Authority

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## Abstract

**Purpose.** Globally, age and some comorbidities have been associated with the risk of more severe outcomes of COVID-19. The purpose of this research is to calculate the hospitalization rate of SARS-CoV-2 positive patients in an Italian Local health Authority (LHA) and to examine whether medical comorbidities encoded through pharmaceutical administrative data are predictors of hospital admission in patients with a positive SARS-CoV-2 naso-pharyngeal swab.

**Methods.** This retrospective observational study was conducted in a LHA of Pescara. Comorbidities were coded through the consumption of drugs, using the WHO's Anatomical Therapeutic Chemical (ATC) classification System. The admission was ascertained by checking the hospital discharge records where generated.

**Results.** During the study period, 1571 patients were tested positive for SARS-CoV-2 oro-and-nasopharyngeal swab. Multivariable logistic analysis showed as predictors of admission an age  $\geq 65$  in the total sample (aOR 10.91; 95%CI 6.86-17.36) as well as in the male (aOR 12.64; 95%CI 6.42-24.87) and female. (aOR 9.27; 95%CI 4.87-17.66) in SARS-CoV-2 positive patients. Comorbidities associated with admission were (GERD) in overall (AdjOR 1.58; 95% CI 1.06-2.34) and male (AdjOR 2.30; 95%CI 1.12-4.72) samples and anticoagulants drugs use in male (AdjOR 3.90; 95% 1.11-13.65) sample, the presence of congestive heart failure (CHF) in female (AdjOR 0.47; 95%CI 0.27-0.83) sample results as protective factor.

**Conclusion.** In conclusion, increasing age, male gender and PPI use are positively associated while female gender and CHF-related drug use are negatively associated with hospitalization in SARS-CoV-2 positive patients. *Clin Ter 2022; 173 (6):528-533 doi: 10.7417/CT.2022.2477*

**Key words:** SARS-CoV-2, Comorbidities, hospitalization rate

## Key points

- Globally, age and some comorbidities have been associated with the risk of more severe outcomes of COVID-19
- increasing age, male gender and PPI use are positively associated with hospitalization in SARS-CoV-2 positive patients
- female gender and CHF-related drug use are negatively associated with hospitalization in SARS-CoV-2 positive patients

## Introduction

After the outbreak reported in China in December 2019, the global spread of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) led the World Health Organization (WHO) to declare the new coronavirus disease 2019 (COVID-19) a pandemic (1).

In the same day Italy counted 15,115 infected people and 1,016 deaths. Rapidly, Italy became the country most affected in the world by the spread of coronavirus. On 1 April in Italy there were 28,403 hospitalized (2).

The signs and symptoms of COVID-19 vary, including fever or chills, cough, shortness of breath, fatigue, muscle or body aches and headache (3-9). The incubation period for COVID-19 is thought to extend to 14 days, with a median time of 4-5 days from exposure to symptoms onset (3,10,11). Currently, the identification of SARS-CoV-2 RNA is mainly conducted by using nasopharyngeal swabs (12).

Since 21 February 2020, when the first case of COVID-19 was recorded in Italy the National Healthcare Service (NHS) were facing a massive burden from the pandemic especially with regard to hospitalizations (13). This led the Local Health Authorities (LHA) to create capacities by canceling elective admissions.

Globally, age and some comorbidities have been associated with the risk of more severe outcomes of COVID-19. (14) Many studies investigated risk factors using severity of disease as an outcome. However, a univocal definition of severe COVID-19 disease is not yet present in literature. Others focused on intensive care unit (ICU) admission of COVID-19 patients and found that those with chronic obstructive pulmonary disease, cardiovascular disease, hypertension, chronic kidney disease, cerebrovascular disease, malignancy, diabetes and immunodeficiency were at higher risk (15, 16). However, these results could be affected by ICU resources, especially because the first months of the pandemic, characterized by the saturation with consequent limited availability of health services, are included in the observation period.

Although there is less evidence available regarding risk factors for hospitalization of COVID-19 patients, different studies performed in different countries are in line: hypertension, heart failure, ischemic heart disease, atrial fibrillation, obesity, diabetes type II and kidney failure have been reported to be risk factors. (17, 18). Furthermore, a study showed that, in addition to some of the aforementioned conditions, dementia and depression are disproportionately common in hospitalized COVID-19 patients (19).

In literature different methods are described for coding patients' comorbidities with administrative data. In fact, it is possible to reconstruct this information through administrative data such as hospital discharge records (20) or through the Defined Daily Doses (DDD) reimbursed (21, 22). The latter method is very useful in outpatient setting.

Recognition of risk factors for hospital admission is important to determine prevention strategies as well as to target high-risk populations for potential therapeutics.

The purpose of this research is to calculate the hospitalization rate of SARS-CoV-2 positive patients in an Italian LHA and to examine whether medical comorbidities encoded through pharmaceutical administrative data are predictors of hospital admission in patients with a positive SARS-CoV-2 naso-pharyngeal swab.

## Methods

### *Study design and patients population*

This retrospective observational study was conducted in a LHA of Pescara, a City of a southern Italy region. The LHA of Pescara provides health services to a population of approximately 350,000 inhabitants. and has three hospitals, a hub and two spokes.

The study period begins with the first hospitalization which took place on February 29th and continues for ten weeks and ends on May 8th.

From the day of the first admission all patients with a SARS-CoV-2 positive pharyngeal swabs until 8 May, 2020 in LHA of Pescara were enrolled in this study. For each patient the first positive swab was taken into consideration, the diagnostic one and not the following ones if present. all patients tested positive for the swab were selected in the study and collected in the company database during the study period. Patient pharyngeal swab specimens were

collected for the SARS-CoV-2 viral nucleic acid detection using real time reverse transcriptase-polymerase chain reaction (RT-PCR) assay. The viral nucleic acid testing for all patients were performed by the laboratory from the Hospital of Pescara, which was designated regional reference laboratory for the research of SARS-CoV-2. The admission was ascertained by checking the hospital discharge records where generated. The outcome considered is hospitalization in a covid ward.

### *Comorbidities coding*

Comorbidities were coded through the consumption of drugs, using the WHO's Anatomical Therapeutic Chemical (ATC) classification System and following the methodology proposed by Prat et al. (22), a validated measure for determining an individual's comorbidity based on their medicine dispensing, developed using therapeutic drug classes and medicinal agents for selected chronic comorbidities.

### *Ethical approval*

The linkage between positive patients and drug consumption was done by the LHA and the authors were given a file in which it was impossible to trace the identity of the patients. The study was conducted in accordance with the Helsinki Declaration.

### *Statistical analysis*

Categorical variables were summarized as frequencies and percentages and continuous variables were described using median and interquartile range (IQR) values. Continuous variables were compared between inpatient and non-hospitalized patients through Mann-Whitney test and the frequencies of categorical variables were compared between two groups using chi-square and Fisher exact test as appropriate. Hospitalizations weekly rate was calculated by dividing the number of subjects with a hospital admission by inhabitant populations of the province of Pescara. All rates were directly standardized for gender and age to the population of province of Pescara and expressed as the number of hospitalizations per 100,000 inhabitants with 95% relative confidence intervals. To assess the association between hospital admission and available factors, a multivariate logistic backward stepwise regression was implemented for overall, male and female samples as follow: admission was considered as dependent variable and each one of the factors at the baseline evaluation were used as independent variables. Adjusted Odds Ratios (Adj-ORs) with their 95% confidence intervals (CIs) were used to measure the association between factors at the baseline and hospital admission. All statistical analysis were performed using STATA 15 software. The test with P value <0.05 were considered statistically significant.

## Results

During the study period 1,571 patients were tested positive for SARS-CoV-2 oro-and-nasopharyngeal swab

Table 1. Sample characteristics

	Overall N(%)	Non Admitted	Admitted N(%)	P value
All	1,571 (100.0)	1,133 (72.1)	438 (27.9)	
Male	712 (45.3)	478 (67.1)	234 (32.9)	<0.001
Female	859 (54.7)	655 (76.2)	204 (23.8)	
Age years median (IQR)	58 (43-77)	53 (38-68)	76 (60-85)	<0.001
Age category				
0-40	345 (22.0)	322 (90.4)	23 (6.6)	<0.001
41-64	598 (38.0)	481 (80.4)	117 (19.6)	
≥65	628 (40.0)	330 (52.5)	298 (47.5)	
Comorbidity				
Antiplatelets	171 (10.9)	78 (45.6)	93 (54.4)	<0.001
Anticoagulants	45 (2.9)	19 (42.2)	26 (57.8)	<0.001
Arrhythmia	38 (2.4)	20 (52.6)	18 (47.4)	0.007
Bipolar Disorder	2 (0.1)	1 (50.0)	1 (50.0)	0.485*
Chronic Airways Disease	60 (3.8)	37 (61.7)	23 (38.3)	0.066
Congestive Heart Failure	159 (10.1)	94 (59.1)	65 (40.9)	<0.001
Depression	64 (4.1)	35 (54.7)	29 (45.3)	0.001
Dementia	17 (1.1)	8 (47.1)	9 (52.9)	0.021
Diabetes	109 (6.9)	49 (45.0)	60 (55.0)	<0.001
Epilepsy	55 (3.5)	30 (54.5)	25 (45.5)	0.003
Gastroesophageal Reflux	135 (8.6)	63 (46.7)	72 (53.3)	<0.001
Gout	28 (1.8)	16 (57.1)	12 (42.9)	0.075
HIV	1 (0.1)	0 (0.0)	1 (100.0)	0.279*
Hyperlipidaemia	93 (5.9)	43 (46.2)	50 (53.8)	<0.001
Hypertension	159 (10.1)	84 (52.8)	75 (47.2)	<0.001
Hyperthyroidism	4 (0.2)	2 (50.0)	2 (50.0)	0.323*
Hypothyroidism	68 (4.3)	48 (70.6)	20 (29.4)	0.773
Ischaemic Heart Disease: angina	16 (1.0)	7 (43.7)	9 (56.3)	0.011
Ischaemic Heart Disease: hypertension	84 (5.3)	42 (50.0)	42 (50.0)	<0.001
Malignancies	12 (0.7)	8 (66.7)	4 (33.3)	0.672
Osteoporosis/Paget's	1 (0.1)	0 (0.0)	1 (100.0)	0.108
Pain	11 (0.7)	6 (54.5)	5 (45.5)	0.192
Psychotic Illness	29 (1.8)	18 (62.1)	11 (37.9)	0.223
Steroid-responsive Disease	7 (0.4)	5 (71.4)	2 (28.6)	1.000
Transplant	1 (0.1)	1 (100.0)	0 (0.0)	1.000

and 438 (27.9%) required hospital admission. Median age of admitted patients were higher than non-admitted group (76 vs 53,  $p<0.001$ ).

Male gender were associated more frequently with admission than female one (32.9% vs 23.8%,  $p<0.001$ ). The description of the data relating to the study sample are summarized in Table 1.

The sex-and-age-adjusted hospitalization rate in the first week amount at 10,3 per 100,000 inhabitant and reached its peak in the third week, with a value of 57,6 per 100,000, more than fivefold compared to the beginning (Table 2).

Multivariable logistic analysis showed as predictors of admission an age  $\geq 65$  in the total sample (aOR 10.91; 95%CI 6.86-17.36) as well as in the male (aOR 12.64;95%CI 6.42-24.87) and female. (aOR 9.27; 95%CI 4.87-17.66) in SARS-CoV-2 positive patients.

Comorbidities associated with admission were (GERD) in overall (AdjOR 1.58; 95% CI 1.06-2.34) and male (AdjOR

Table 2. Sex-and-Age-Adjusted Hospitalization rate per 100,000 inhabitant in the study period

Week	adjusted rate	95% CI
1	10.3	(8.7-11.9)
2	16.8	(15.8-17.9)
3	57.6	(54.3-60.9)
4	42.9	(40.0-0,45)
5	25.6	(23.4-27.8)
6	29.7	(26.0-33.3)
7	17.2	(15.0-19.4)
8	14.0	(13.1-14.8)
9	12.0	(11.2-12.7)
10	11.0	(10.8-11.2)

Table 3. Multivariable logistic analysis results

	Overall	Female	Male
Male vs Female	1.77 (1.38-2.26)		
Age cat			
0-40	Ref	Ref	Ref
41-64	3.24 (2.02-5.19)	2.70 (1.39-5.23)	3.85 (1.96-7.54)
≥65	10.91 (6.86-17.36)	9.27 (4.87-17.66)	12.64 (6.42-24.87)
Comorbidity			
Antiplatelets	-	1.53 (0.90-2.61)	
Anticoagulants	1.68 (0.90-3.15)		3.90 (1.11-13.65)
Arrhythmia	-	2.07 (0.83-5.14)	0.23 (0.07-0.79)
Bipolar Disorder	-		
Chronic Airways Disease	-		
Congestive Heart Failure	-	0.47 (0.27-0.83)	
Depression	-	1.73 (0.82-3.64)	
Dementia	-		
Diabetes	1.46 (0.96-2.24)		1.65 (0.89-3.10)
Epilepsy	-		2.56 (0.84-7.81)
Gastrooesophageal Reflux	1.58 (1.06-2.34)		2.30 (1.12-4.72)
Gout	-		
HIV	-		
Hyperlipidaemia	-		
Hypertension	-	1.63 (0.97-2.75)	
Hyperthyroidism	-		
Hypothyroidism	-		
Ischaemic Heart Disease: angina	-		
Ischaemic Heart Disease: hypertension	-		
Malignancies	-		
Osteoporosis/Paget's	-		
Pain	-		
Psychotic Illness	-	0.40 (0.13-1.26)	
Steroid-responsive Disease	-	-	-
Transplant	-	-	-

2.30; 95%CI 1.12-4.72) samples and anticoagulants drugs use in male (AdjOR 3.90; 95% 1.11-13.65) sample, the presence of congestive heart failure (CHF) in female (AdjOR 0.47;95%CI 0.27-0.83) sample results as protective factor. The results of the multivariate analysis are summarized in Table 3.

## Discussion

This study examined the hospital admissions of patients with SARS-CoV-2 positive swabs occurred in a period of 10 weeks from the first admission to the LHA in Pescara, a province of a region of southern Italy with about 350,000 inhabitants. The hospitalization rate increased rapidly in the first 3 weeks by fivefold, committing an enormous amount of resources in a short time and requiring rapid organizational changes. In the third week of the study, the peak of hospitalizations was reached and from the fourth week onwards there was a slow decrease. This decrease can be ascribed to

the intervention by the Italian government which through it provided for the adoption of strict rules to decrease individual mobility and increase social distances, accompanied by the use of personal protection measures such as masks and gloves, such measures due to their rigidity they have taken the name of “lockdown” and which became mandatory on March 11, 2020. The effectiveness that lockdown measures can have on reducing the contagion is described and known (23) and such measures in the absence of authorized vaccines and specific therapies represented an adequate preventive strategy even if extreme and accepting the economic and social consequences (24).

This study shows the association between increasing age and male gender and hospitalization in SARAS-CoV-2 positive patients.

This results are largely confirmatory of the literature, indeed increasing age, and male gender were have been related to an increased risk of hospitalization (25) and independently associated with higher in-hospital mortality and in general worse in-hospital outcomes (26).

This study shows an association between GERD disease and hospitalization in positive SARS-CoV-2 patients in the total sample and in the male sample. GERD was codified by controlling drug use in the previous year as proposed by Prat et Al (22).

The use of proton pump inhibitors (PPIs) in the literature has been related to COVID-19 positivity (27), increased risk for severe clinical outcomes of COVID-19 (28) as a negative predictive factor for development of secondary infections and consecutive ARDS in patients with COVID-19 (29).

Although more studies are needed to investigate the association between PPI use and COVID-19, prescribing PPIs needs to evaluate benefit-risk assessments during the pandemic.

Our study shows that the use of CHF drugs in women is a protective factor for hospitalization in SARS-CoV-2 positive patients. The drugs used in the treatment of CHF are predominantly diuretics. The literature has associated a protective role of some diuretics, such as spironolactone, against the COVID-19 syndrome (30). Indeed, the presence of angiotensin-converting enzyme-2 (ACE2) receptor and transmembrane serine protease 2 (TMPRSS2) is mandatory for SARS-CoV-2 cell entry, while ACE2 and TMPRSS2 expression may modulate its infectivity (31-33). ACE2 and TMPRSS2 altered expressions can be concomitantly addressed by spironolactone and other mineralocorticoid antagonists, due to their actions in the renin-angiotensin-aldosterone system (RAAS) and as androgen antagonists, respectively, providing potential protection against SARS-CoV-2. Spironolactone has demonstrated actions that may provide protection during SARS-CoV-2 infection, since it may reduce SARS-CoV-2 infectivity, inhibit cytokine and inflammatory storm as an overresponse to the virus, and alleviate lung, heart, and kidney injuries (30).

The results of this study should be considered in light of one important limitation. Indeed, the administrative data used lack clinical information such as laboratory results and symptoms. This can lead to unmeasured confounding factors that hinder multivariate analysis.

The strength of this study consists in having demonstrated the usefulness of administrative data to predict which pathologies inferred from the use of drugs are associated with a greater possibility of hospitalization. Moreover, it is the first Italian study that used the flow of drugs to encode the comorbidities that preceded the infection with the SARS-CoV-2 virus and that they related to hospitalization, which still represents an index of disease severity. However, other research with more solid study designs and larger samples are needed to investigate the link between the use of drugs due to certain diseases and the outcomes related to SARS-CoV-2 infection.

In conclusion, increasing age, male gender and PPI use are positively associated while female gender and CHF-related drug use are negatively associated with hospitalization in SARS-CoV-2 positive patients. The use of administrative data held by the LHA could be useful in identifying patients at greater risk and planning targeted and strategic prevention interventions during the pandemic.

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