# COVID-19 mortality risk factors in older people in a long-term care center.

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# Abstract

**Objectives:** Despite high rates of COVID-19 infection and increased related mortality have been reported among older adults admitted in long-term care facilities, a limited amount of information is available about the natural course of this pandemic and prognostic factors in this population. In the current study, we aimed to investigate the epidemiologic, demographics, clinical, or therapeutic factors that may predict the prognosis in a cohort of COVID-19 infected elderly in a nursing home.

**Methods:** We conducted a retrospective analysis of all COVID-19 confirmed institutionalized elderly in a nursing home transformed into a reference intermediate healthcare facility from March 15 to June 5, 2020. Epidemiological, demographic, and frailty status before infection, and clinical, laboratory, treatment, and outcome data during infection were collected. We used bivariate analysis and multivariate logistic regression to identify risk factors for mortality.

**Results:** The analysis comprised all 100 COVID-19 confirmed cases during the study period. The median age was 85 years; 62% were female. The case fatality rate was 20%. In the bivariate analysis, male gender, fever, respiratory symptoms, severe cognitive decline, a low Barthel index, and lymphocytopenia were significantly associated with mortality. Multivariate logistic regression analysis identified male gender, low Barthel index, no pharmacological treatment, and lymphocytopenia as independent risk factors associated with mortality.

**Conclusions and Implications:** Male gender, low Barthel index, no pharmacological treatment and lymphocytopenia are independent risk factors for COVID-19 mortality in institutionalized elderly patients in long-term care nursing homes. Treatment with hydroxychloroquine and azithromycin was associated with lower mortality in these patients.

# Introduction

While a great deal of information regarding the evolution of patients with COVID-19 infection[1-10] has been recorded since the onset of novel coronavirus pandemic in hospitals over the world, only a few data have been published up to date regarding the curse of the disease in patients admitted in long-term care facilities[11].

Studies by McMichael T.M. and Aron MM[11,12] 1from a long-term care facility suggests that nursing home populations (e.g., older adults often with underlying chronic medical conditions) could be especially vulnerable to SARS-CoV-2 infection and at higher risk for COVID-19 associated morbidity and mortality.

In the current study, we aimed to provide information about the clinical evolution of elderly patients infected by COVID-19 admitted in nursing homes and to identify prognostic mortality factors in such a population.

The study was approved by the Research Ethics Committee of the Andorran Healthcare Services.

# Methods

## Study design

The study was performed at a public nursing home from March 15 to June 5, 2020, identifying all the COVID-19 confirmed patients. This reference nursing home was transformed into a COVID-19 center for the admission of institutionalized seniors considered probable or confirmed cases of COVID-19 from the same center or other nursing homes. To this end, a joint action strategy was settled with the other nursing homes in the country, establishing a referral circuit to support them in the event of an outbreak of COVID-19 disease in their institution. Within 72 hours of detecting the first COVID case, 35 residents were moved to a hotel to prevent further spread following medical criteria (residents with a low level of functional and cognitive dependence were transferred). In the different serological and PCR controls carried out, only three residents housed in the hotel had COVID-19 infection, and the mortality in this population was null.

## Data collection

The following data were recorded for all patients: age, sex, date of admission, mean stay, the origin of the patient, dementia stage, Barthel index, Charlson comorbidity index, previous flu vaccination, clinical presentation, laboratory results, treatment, RT-PCR for SARS-CoV-2, hospital referral, mortality rate, and case fatality rate.

## Definitions

Four categories of the patient's origin were defined: the reference nursing home, other nursing homes, home, or hotel.

Dementia was measured by the Global Deterioration Scale (GDS), developed by Dr. Reisberg[13], which consists of seven stages. 1: no cognitive decline, 2: very mild cognitive decline, 3: mild cognitive decline, 4: moderate cognitive decline, 5: moderately severe cognitive decline, 6: moderately severe decline, 7: very severe cognitive decline.

Barthel index[14] is an ordinal scale of functional capacity used to measure performance in daily living activities, with values ranging from 0 (totally dependent) to 100 (totally independent). Proposed guidelines for interpreting Barthel index are: 0-15: totally dependent, 20-35: very dependent, 40-55: partially dependent, 60-75: minimally dependent, 80-100: totally independent[15].

Underlying diseases were considered as the presence of comorbid illness with the age-adjusted Charlson comorbidity index[16], which predicts ten-year survival in patients with multiple comorbidities.

Patients were grouped into three clinical categories: asymptomatic, respiratory symptoms (rhinitis, pharyngitis, cough, expectoration, and dyspnea) and digestive symptoms (diarrhea). Fever was defined as an axillary temperature of at least 37.5°C.

An analytical control was carried out, at least, on the admission and the discharge, recording the presence of lymphocytopenia, anemia, and or thrombocytopenia. Inflammation markers such as CRP, Ferritin, Dimer D, LDH, and troponin were also collected. Lymphocytopenia was defined as a total lymphocyte count of less than $1.0 \times 10^9$/L (1000/μL) and thrombocytopenia as a platelet count of less than $150 \times 10^3$ per μL. The diagnosis of anemia in men was based on a hemoglobin of less than 13 to 14 g/dL; in women, less than 12 to 13 g/dL.

As for the treatment, five categories were defined: patients who received hydroxychloroquine and azithromycin, only hydroxychloroquine, hydroxychloroquine plus another antibiotic, beta-lactam, or quinolone antibiotics, and no treatment.

We also recorded the percentage of patients with two consecutive (48 hours apart) negative molecular detection results for SARS-CoV-2 from a nasopharyngeal swab after 14 days of treatment with hydroxychloroquine and azithromycin.

Patients whose symptoms resolved and who had two consecutive (48 hours apart) RT-PCR for SARS-CoV-2 negative were considered successfully treated and cured[17].

Four categories of discharge destination were defined: reference nursing home in non-COVID areas, other nursing homes, home, or death.

The mortality rate associated with COVID-19 in the center was considered as the death rate in the reference nursing home population.

The case fatality rate in the reference nursing center is the proportion of deaths from a COVID-19 disease compared to the total number of people diagnosed with the disease admitted in the center.

## Statistical analysis

A statistical study has been carried out to identify risk factors for mortality in patients with COVID 19. Bivariate tests have been performed between the qualitative and quantitative variables and the successfully treated variable COVID (yes / no). A chi-squared test was used for categorical variables and the t-test/Mann-Whitney test for quantitative variables. Additional bivariate analyses were performed to compare subject characteristics between treatment groups, in order to identify possible confounders. Variables with a p-value lower than 0.05 were included in a multivariate logistic regression model[18] to identify independent predictors of mortality. The final model was obtained after removing all non-statistically significant variables (backward selection procedure). Furthermore, a second multivariate regression model was adjusted, including only baseline variables to obtain a score to predict mortality independently of the effect of pharmacological treatment. ROC curves have been obtained to evaluate the fit of the models, and the AUC has been calculated. The best cut-off point has been determined, and sensitivity and specified values have been obtained. Statistical analyses were performed with the SAS

system version 9.4 (SAS Institute Inc., Cary, North Carolina, USA). The statistical significance level was set at 0.05.

## Data availability

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

# Results

The study group comprised 100 COVID-19 confirmed cases with a mean age of 85 (IQR 65-103) years. Sixty-two percent were female, and the average length of stay was 22 days. Fifty-two patients were initially from the reference nursing home, 36 came from other nursing homes, nine from home, and three comings back from the hotel.

According to the global deterioration scale for the assessment of primary degenerative dementia, 73% of patients presented dementia, and 91.6% of dead had severe dementia (GDS6- GDS7). Seventy-six percent of patients had some level of functional dependence (Figure 1). Clinically, 57% had respiratory symptoms, and 39% overcome the infection without any symptoms. Blood tests revealed anemia in 36 cases and lymphocytopenia in 38 patients.

Eighty-three percent received pharmacological treatment, mostly with hydroxychloroquine and azithromycin (70%) (Figure 2). Only five patients had diarrhea as a side effect related to hydroxychloroquine. Cardiac monitoring was performed by electrocardiogram, and no rhythm changes were observed with this treatment in any patient.

After 14 days, 12 patients had two negative molecular detection results for SARS-CoV-2 from a nasopharyngeal swab. Seventy-six patients were considered cured, and 24 died, of which four happened in the reference hospital. Thirty-five patients were discharged to non-COVID areas of Cedre's nursing home, 31 to other nursing homes, and nine to home.

The mortality rate associated with COVID-19 only for the original residents of the reference nursing center was 14% (18 death/125 residents). The overall case fatality rate at the reference nursing home was 20% (20 death/100 COVID-19 residents).

In the bivariate analysis, the following factors showed a significantly greater risk of mortality among COVID-19 patients: male-gender, fever, respiratory symptoms, pharmacological treatment, type of treatment, serum therapy, oxygen therapy, dementia, Barthel indelymphocytopenia, LDH, and D-dimer (Table 1).

No statistically significant differences were observed in Charlson's index, treatment started within 24 hours, anemia, low platelet count, ferritin, CRP, troponin levels, or previous flu vaccination.

Table 2 shows the results of the bivariate analysis results between treatment groups. Only 'treatment started within 24 hours' was found statistically imbalanced between groups, but we did not find any relation between this variable and mortality. Temperature, serum therapy and D-dimer presented some differences between groups, although not statistically significant.

In the multivariate regression analysis, the independent risk factors associated with a higher COVID-19 related mortality were: male-gender, type of treatment, Barthel index, and lymphocytopenia (Table 3). Although statistically significant differences were observed between LDH, D-dimer and mortality values in the bivariate analysis, (as their levels increase, the risk of mortality increases) they were not included in the multivariate logistic regression due to the high number (20%) of missings in these two parameters. A second multivariate analysis was performed including treatment started within 24 hours, temperature and serum therapy, and similar results as in the initial multivariate analysis were obtained.

In order to obtain a score that allows predicting COVID-19 evolution from baseline, a new model was adjusted, excluding pharmacological treatment.

To calculate a prognostic score, the following formula was used:

Score= 1.4* (Sex= "Male") − 0.04* Barthel + 0.9* (Lymphopenia= "Yes")

The higher the score, the higher was the probability of dying. We obtained an AUC of 0.85 (Figure 3). The cut-off point that best ranks between patients who are successfully treated and those who are not cured is 0.2, meaning all those patients with a score higher than 0.2 are most at risk of dying, with a specificity of 79.7% and a sensitivity of 80.0%.

## Discussion

With the outbreak of COVID-19, the Andorran Healthcare Service acted quickly and proactively to control the pandemic in nursing homes. The early reaction transforming the reference nursing home into an intermediate healthcare facility and moving to a hotel 35 healthy residents from this center with a low level of functional and cognitive dependence, probably avoided excess mortality since none of the people transferred to the hotel died. One hundred COVID-19 elderly patients were admitted to the reference intermediate care nursing home, and they received the same care as they would get in hospital wards, 76% of cases were cured. The case fatality rate in those remaining in the nursing home was lower (20%) than that reported in other settings (34%)[11,12] despite being mostly patients with high functional dependence. Seven patients were referred to a tertiary care hospital for presenting medical criteria for mechanical respiratory ventilation.

As far as we know, this is the first reported study describing how a nursing home was transformed in an intermediate care facility to face the COVID-19 outbreak and analyzing which prognostic factors could predict infection-related mortality in this segment of the elderly population, despite the deployment of a significant amount of medical resources.

Several factors related to gender, respiratory symptoms, supportive and specific therapy, cognitive and functional deterioration, and inflammatory and immune factors were associated with mortality in the bivariate analysis. In the multivariate logistic regression analysis, only male-gender, Barthel index, lymphocytopenia, and hydroxychloroquine plus azithromycin were identified as independent factors for mortality. Variables that presented more differences between treatment groups were included in a second multivariate model to evaluate potential confounding factors, and similar results were obtained.

Many reports have outlined that, despite rates of infection are similar among men and women, men are at higher risk of death from the COVID-19 infection[3,19]. The explanation for that phenomenon is unclear, although previous studies have suggested that women are less susceptible to viral infection possibly, because of the protection of X chromosome and sex hormones, which play an essential role in innate and adaptive immunity[20].

The institutionalized elderly present a cognitive and functional decline that may worsen with acute illness such as COVID-19 [21]. This study reveals a direct relationship between decreased functional capacity measured by the Barthel index and mortality. Functional status in older people has been identified as a prognostic mortality factor in respiratory infections[22]. The current study is the first to prove a direct relationship between the Barthel index and mortality in COVID-19 infected patients.

Contrary to what was expected, we did not find any relationship between clinical comorbidity and death in these patients, a factor that is usually present in studies evaluating mortality for other causes in older people [23-25] , and that it was also relevant in previous reports of COVID-19 infection in China[5,6,26]. Besides, flu vaccination also had no impact on mortality.

The other independent risk factor detected was lymphocytopenia, a common finding in COVID-19 infected patients that has been previously related to mortality [4,27,28]. This could be due to a direct effect of the virus or the consequence of the cytokine-mediated inflammatory cascade inducing lymphocytes migration [27]. In any case, T-lymphocytes deficiency or dysregulation may reflect oversized immune reactions that can contribute to disease severity and mortality[29].

Regarding the treatment, hydroxychloroquine and azithromycin were prescribed for five days as the initial treatment for all patients. Before and during this initial treatment period, electrocardiograms were performed to monitor patient's tolerance to the treatment. When this pharmacological combination was contraindicated based on electrocardiographic alterations, either hydroxychloroquine alone or beta-lactams were prescribed instead.

It is worth highlighting that the multivariate logistic regression analysis identified hydroxychloroquine plus azithromycin treatment as an independent factor favoring survival compared with no treatment or other treatments. At present, contradictory results have been published regarding the effectiveness of this treatment in COVID-19 infected patients and the associated risk of adverse events using those medications [30-34]. It might be possible that this treatment could only work when used early and in a

particular group of patients with similar specific characteristics as in the present study. In any case, only randomized clinical trials could definitively clear these uncertainties.

Using only those independent risk factors identified in the multivariate analysis, which could be easily collected at onset of the disease infection, we have elaborate a score that, beyond the potential beneficial effect of pharmacological treatment, may be able to predict mortality with reasonable specificity and sensitivity.

This study has some limitations. First, it is a retrospective study, and some missing laboratory date precluded to include LDH and D-dimer parameters in the multivariate regression analysis. Second, the advanced age of all patients included has probably been prevented from identifying this parameter as a prognostic factor for death. Third, the high prevalence of dementia and functional dependence among the patients included may have generated results that might not be precisely reproducible in other cohorts of elderly patients with better functional capabilities. Finally, it would be interesting to evaluate the presence of interactions between variables. A bigger sample size would be required.

# Conclusion

In summary, this study describes the feasibility of transforming a nursing home into an intermediate healthcare facility to face an epidemic outbreak of COVID-19 in this setting and limiting referrals to a tertiary care hospital. For taking care of those COVID-19 infected older people, the independent prognostic factors identified in the present study can be of enormous help to adjust the adequate healthcare resources provision and for limitation of therapeutic efforts in case of new outbreaks of the pandemic.

# Declarations

### Acknowledgements
We respectfully and sincerely thank all front-line healthcare workers from the reference nursing home for their hard work and sacrifice in the face of this outbreak.

### Contributors
EH contributed to the study design, data collection, interpretation of the data, writing and revising the manuscript and accepts responsibility for the corresponding author. PG, MB, JC, YC, EG, OM, MA, JM, PL, RL contributed to the data collection, data interpretation, and revising of the manuscript. OV led the data analysis, data interpretation, and editing of the manuscript. JP contributed to the interpretation of the data, writing, and revising of the manuscript. All authors read and approved the final manuscript.

### Declaration of interests
We declare no competing interests.

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# Tables

Table 1 Risk factors associated with COVID-19 mortality on bivariate analysis. % (N) for categorical variables and means (sd) for quantitative (*)

| Variable | Cured | No cured | P-Value |
|---|---|---|---|
| Sex - Male | 28.9 (22) | 66.7 (16) | <0.001 |
| Age * | 86.5 (7.6) | 86.1 (8.9) | 0.888 |
| Flu vaccine | 78.9 (60) | 66.7 (16) | 0.219 |
| Temperature> 37,5º | 52.6 (40) | 79.2 (19) | 0.021 |
| Respiratory symptoms | 50.0 (38) | 79.2 (19) | 0.012 |
| H[a] side effects | 2.8 (2) | 13.0 (3) | 0.090 |
| Treatment H+A[a] | 81.6 (62) | 33.3 (8) | <0.001 |
| H[b] | 7.9 (6) | 12.5 (3) | |
| No treatment[c] | 10.5 (8) | 54.2 (13) | |
| Treatment started in the first 24 h | 39.5 (30) | 37.5 (9) | 0.863 |
| Serum therapy | 43.4 (33) | 79.2 (19) | 0.002 |
| Oxygen therapy | 50.0 (38) | 95.8 (23) | <0.001 |
| Severe cognitive decline (GDS 5-7) | 67.1 (51) | 91.7 (22) | 0.018 |
| Charlson * | 5.7 (2.0) | 6.0 (2.5) | 0.183 |
| Barthel index * | 43.3 (39.9) | 18.8 (23.6) | 0.021 |
| Severe/totally dependency (Barthel ≤60) | 65.8 (50) | 91.7 (22) | 0.014 |
| Ferritin (log) * | 6.0 (1.1) | 6.6 (1.3) | 0.106 |
| LDH (log) * | 6.2 (0.3) | 6.4 (0.4) | 0.033 |
| Anemia | 43.2 (32) | 26.7 (4) | 0.233 |
| Lymphocytopenia | 37.8 (28) | 66.7 (10) | 0.040 |
| Thrombocytopenia | 25.7 (19) | 33.3 (5) | 0.542 |
| D DIMER (log) * | 0.31 (0.86) | 1.04 (0.97) | 0.015 |
| CRP (log) * | 3.2 (1.6) | 4.1 (1.4) | 0.063 |
| Troponin (log) * | 3.5 (0.7) | 4.4 (1.1) | 0.092 |

H+A[a]: Hydroxychloroquine and Azithromycin.

H[b]: Hydroxychloroquine.

No treatment [c] includes Others: Beta-lactam or Quinolone antibiotics.

Table 2 Bivariate analysis with treatment. % (N) for categorical variables and means (sd) for quantitative (*)

| Variable | H+A[a] | H[b] | No treatment | P-Value |
|---|---|---|---|---|
| Sex - Male | 37.1 (26) | 22.2 (2) | 47.6 (10) | 0.407 |
| Age * | 86.3 (7.3) | 88.3 (8.1) | 85.9 (9.6) | 0.727 |
| Flu vaccine | 75.7 (53) | 100 (9) | 66.7 (14) | 0.146 |
| Temperature> 37,5º | 54.3 (38) | 55.6 (5) | 76.2 (16) | 0.197 |
| Respiratory symptoms | 55.7 (39) | 66.7 (6) | 57.1 (12) | 0.823 |
| H[b] side effects | 6.1 (4) | 12.5 (1) | 0 (0) | 0.227 |
| Treatment 24 h | 48.8 (34) | 11.1 (1) | 19.0 (4) | 0.021 |
| Serum therapy | 45.7 (32) | 77.8 (7) | 61.9 (13) | 0.105 |
| Oxygen therapy | 57.1 (40) | 77.8 (7) | 66.7 (14) | 0.409 |
| Severe cognitive decline (GDS 5-7) | 70.0 (49) | 77.8 (7) | 81.0 (17) | 0.578 |
| Charlson * | 5.7 (2.1) | 5.7 (2.5) | 5.9 (2.1) | 0.876 |
| Barthel index * | 41.4 (40.8) | 20.0 (18.7) | 31.7 (32.6) | 0.407 |
| Ferritin (log) * | 6.0 (1.1) | 6.3 (1.1) | 5.8 (1.4) | 0.961 |
| LDH (log) * | 6.2 (0.4) | 6.4 (0.5) | 6.2 (0.2) | 0.508 |
| Anemia | 40.3 (27) | 50.0 (4) | 35.7 (5) | 0.806 |
| Lymphocytopenia | 41.8 (28) | 37.5 (3) | 50.0 (7) | 0.813 |
| Thrombocytopenia | 20.9 (14) | 50.0 (4) | 42.9 (6) | 0.088 |
| D DIMER (log) * | 0.30 (0.9) | 1.01 (1.1) | 0.70 (1.0) | 0.102 |
| CRP (log) * | 3.4 (1.6) | 3.5 (1.8) | 3.6 (1.8) | 0.895 |
| Troponin (log) * | 3.6 (1.8) | 3.9 (1.8) | 3.5 (1.6) | 0.822 |

H+A[a]: Hydroxychloroquine and Azithromycin.

H[b]: Hydroxychloroquine.

No treatment [c] includes Others: Beta-lactam or Quinolone antibiotics.

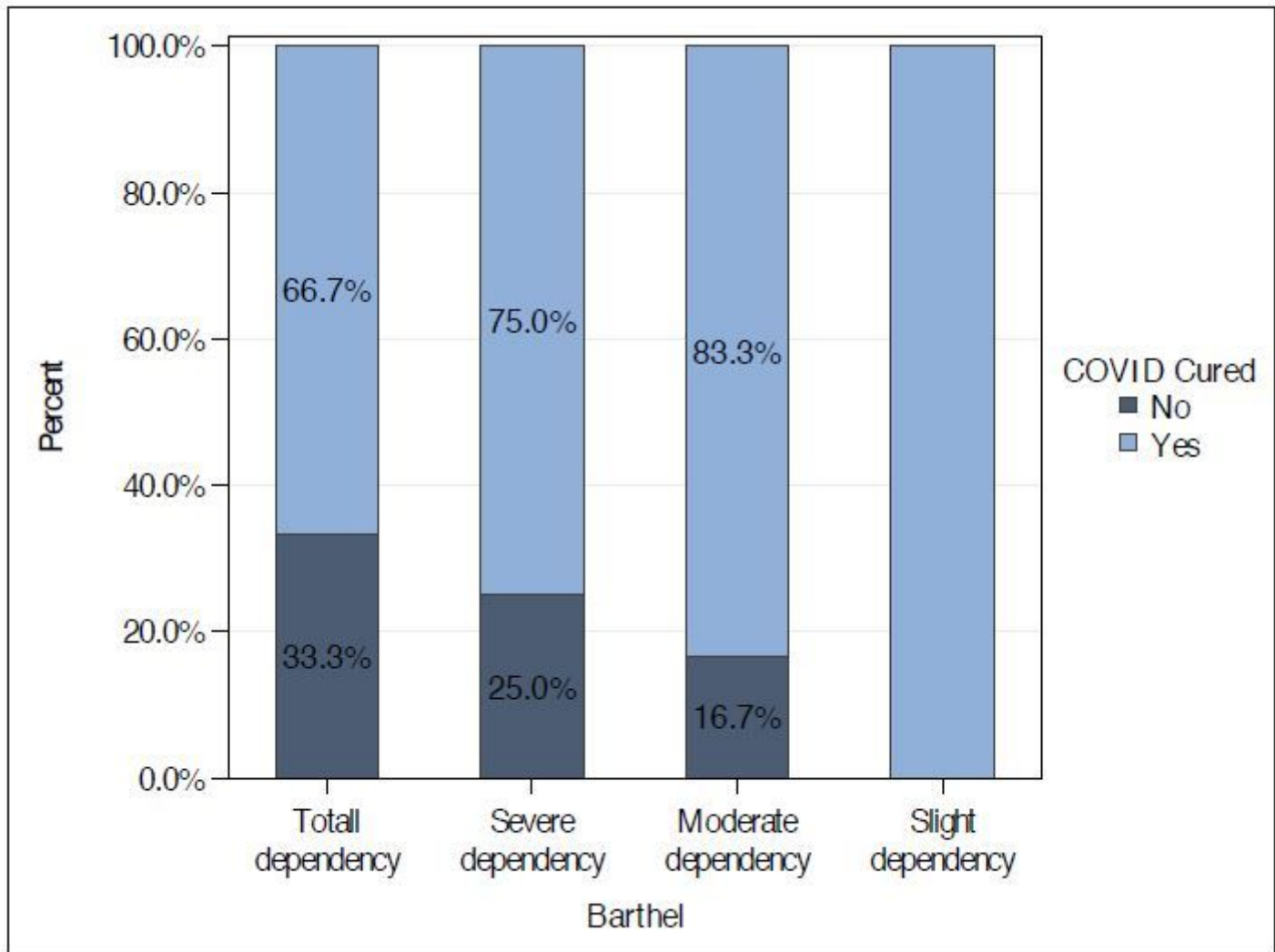
Table 3  Risk factors associated with COVID-19 mortality on multivariate analysis

| Variable | B (SE) | OR | P-Value |
|---|---|---|---|
| Sex - Male | 3.37 (1.01) | 38.1 | 0.001 |
| Treatment H+A[a] | -3.12 (1.04) | 0.044 | 0.004 |
| Treatment H[b] | -1.13 (1.25) | 0.32 | 0.369 |
| Barthel's index | -0.047 (0.017) | 0.92 | 0.006 |
| Lymphopenia | 1.88 (0.92) | 6.55 | 0.039 |

H+A [a]: Hydroxychloroquine and Azithromycin.

H [b]: Hydroxychloroquine.

Treatment considers 'No treatment' as reference

# Figures

## Figure 1

Functional capacity and percentage of COVID-19 patients cured.

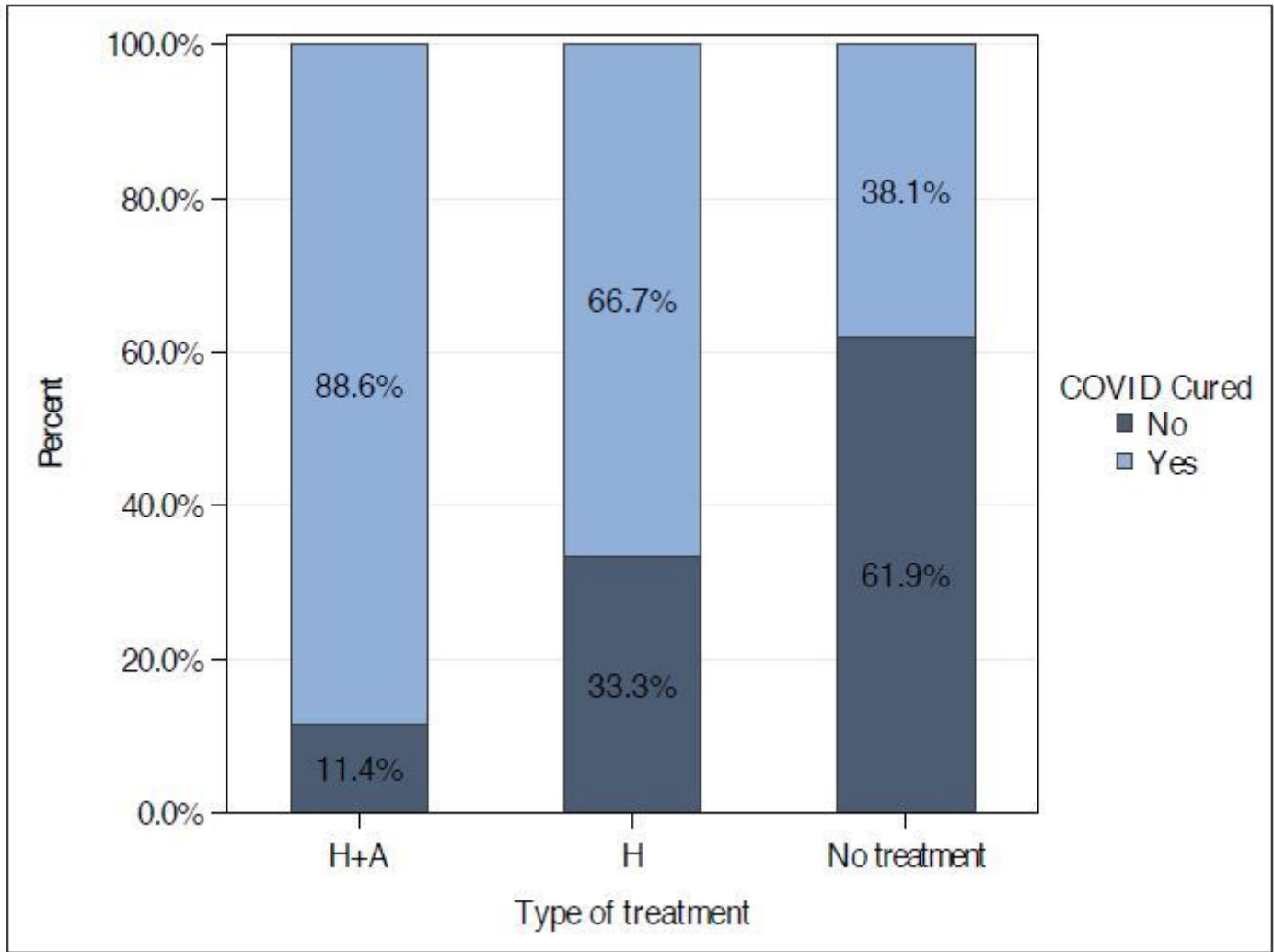



**Figure 2**

Type of treatment and percentage of COVID-19 patients cured. H+A: Hydroxychloroquine and Azithromycin. H: Hydroxychloroquine. No treatment includes Others: Beta-lactam or Quinolone antibiotics.

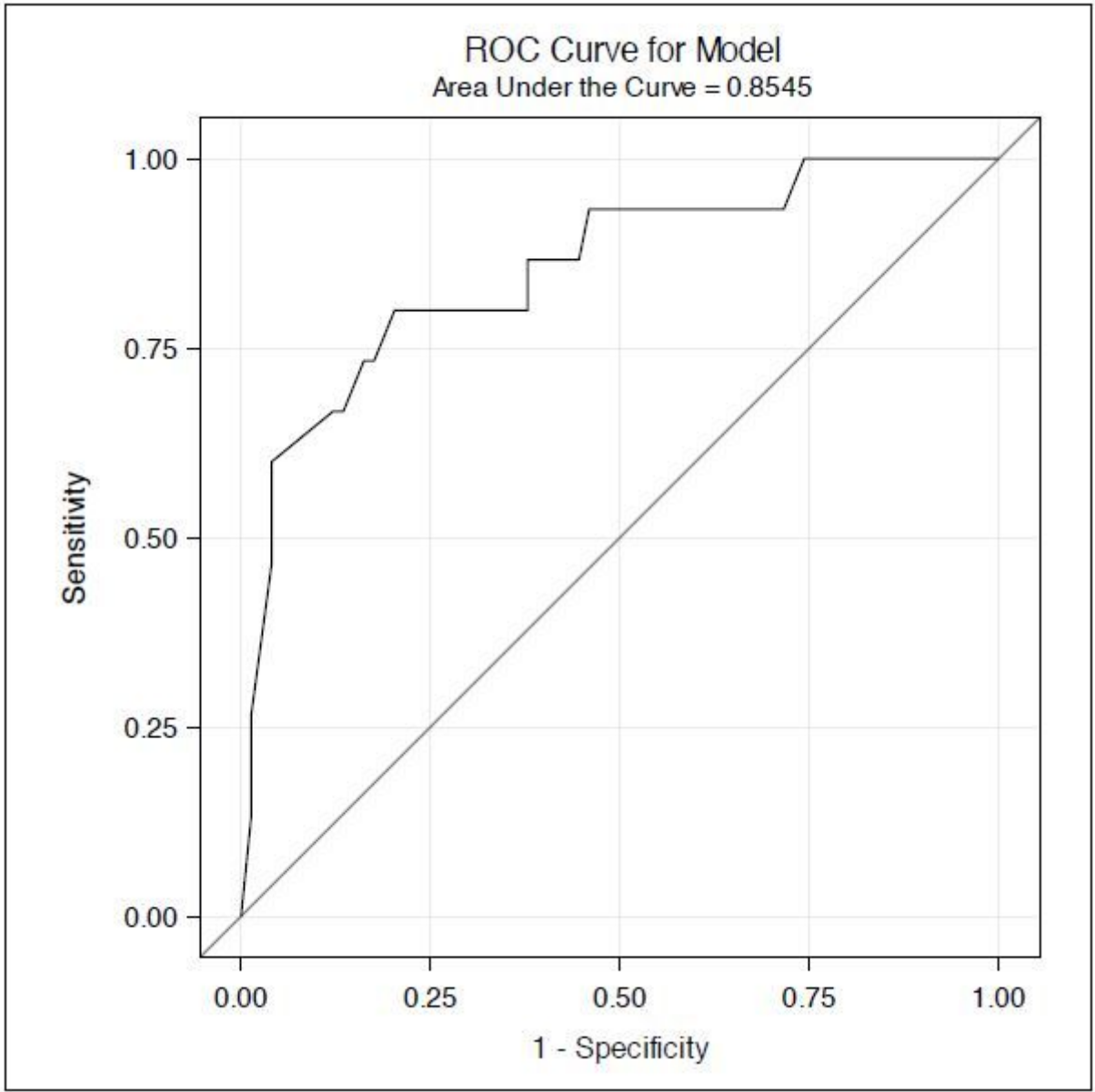



**Figure 3**

Prognostic COVID-19 mortality score-ROC Curve for Model