COVID-19: Clinical Presentation and Prognostic Factors of Severe Disease and Mortality in the Oldest-old Population. A Cohort Study.

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Research Article

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Abstract

INTRODUCTION

The oldest-old population (80 years or older) has the highest lethality from COVID-19. There is little information on the clinical presentation and specific prognostic factors for this group. This trial evaluated the clinical presentation and prognostic factors of severe disease and mortality in the oldest-old population.

METHODS

Ambispective cohort study of oldest-old patients hospitalized for respiratory infection associated with COVID-19 and with a positive test by real-time polymerase chain reaction. The clinical presentation and the factors associated with severe disease and mortality were evaluated (logistic regression). All patients were followed until discharge or death.

RESULTS

A total of 103 patients (59.2% female) were included. The most frequent symptoms were fever (68.9%), dyspnoea (60.2%), and cough (39.8%), and 11.7% presented confusion. Fifty-nine patients (57.3%) presented severe disease, and 59 died, with 43 patients (41.7%) presenting both of these. In the multivariate analysis, male sex (OR 0.31, 95% confidence interval [95% CI] 0.13-0.73, p 0.0074) and serum lactate dehydrogenase (LDH) (OR 2.55, 95% CI 1.21-5.37, p 0.0139) were associated with severe disease, and serum sodium was associated with mortality (OR 3.12, 95% CI 1.18-8.26, p 0.0222). No chronic disease or pharmacological treatment were associated with worse outcomes.

CONCLUSIONS

The typical presenting symptoms of respiratory infection in COVID-19 are less frequent in the oldest-old population. Male sex and LDH level are predictors of severe disease, and serum sodium level predicts of mortality in this population.

Introduction

The pandemic caused by the new severe acute respiratory distress syndrome coronavirus (SARS-CoV-2) represents a priority objective of current medical research given its global extent. The older population has the highest lethality, having reported a crude fatality ratio of 12%, and this is much higher (approximately 30%) in the oldest-old people (80 or more years old) ([1,2]. Given this population's greater vulnerability, knowledge of this pathology in them is a priority.

Proper management of affected oldest-old people requires knowledge of the clinical presentation and prognostic factors specific to this group. Most diseases, including infectious diseases, usually include
atypical presentations, especially in this population [3–5], and their clinical profile means that the prognostic factors identified in the general adult population cannot be extrapolated.

Data on clinical presentation and prognostic factors have been reported in cohorts of older population [6]. However, most of these are from Asian populations and have a fairly low age cut-off (60-65 years), leaving the oldest-old population underrepresented. The results of these studies cannot be extrapolated to the oldest-old population of our environment [7] since the level of autonomy and physical activity of the 60-70-year-old group are more similar to those of the youngest than the oldest patients [7,8].

There are few studies specifically reporting on clinical presentation and prognostic factors in the oldest-old population[9–11]. The main reported symptoms of clinical presentation have included fever, dyspnoea, cough, and deterioration of functional status; and factors associated with higher mortality included age, male sex, severe functional dependence, cognitive decline, renal function, and inflammatory markers. However, other relevant variables like previous pharmacologic treatments or other important outcomes as severe disease have not been specifically evaluated in this population.

In the present study, we analysed the clinical presentation and the most important prognostic factors of severe disease and mortality in a cohort of oldest-old people (aged 80 years or more) hospitalized for COVID-19.

**Methods**

**Design and sample**

The present work is a cohort study based on the previously described ambispective cohort (n=464) of patients hospitalized for COVID-19 in the hospitals of the Consorci Sanitari de l'Alt Penedès i Garraf (CSAPG) [12]. The CSAPG includes three second-level hospitals with a total of 457 hospital beds, including seven intensive-care beds (extended to 24 beds at the peak of the epidemic) and 182 intermediate-care beds. Its territorial scope includes an area of Barcelona with a reference population of 247,357 inhabitants.

For this study, patients aged 80 or older who were admitted for respiratory infection associated with COVID-19 and with pharyngeal, nasal, or sputum smears positive for SARS-CoV-2 (real time-polymerase chain reaction [RT-PCR]) were included. All patients who were hospitalized through the emergency department were recruited from March 12 to May 2, 2020 and were followed until hospital discharge or death. Patients with a positive COVID-19 test but without clinical or radiological respiratory involvement and patients with compatible respiratory symptoms who were treated as COVID-19 patients during admission but with negative smears (“COVID-19 clinical”) were excluded. Also excluded were patients who, despite meeting the diagnostic inclusion criteria, were not admitted to a hospitalization unit (for example, due to death in the emergency department or transfer to a tertiary referral centre). In our case, there was no need to transfer patients to other centres of the same level for lack of hospital beds.
Patients were selected from the daily hospitalization census. This census included the medical diagnosis of admission of each patient and a signal that identified the patients who had requested an RT-PCR test for SARS-CoV-2.

A predetermined calculation of the sample size was not performed. We included all possible patients who met the admission criteria.

**Variables and information collection**

Information on the variables was collected from the computerized medical records (GoWin program, version 2.4.0). The interviewers (the COVID-19 research group of the CSAPG [30 people]) began the study on April 6 and continued until the discharge or death of the last patient recruited. The information was collected with the help of two data collection notebooks (the first for baseline assessment and the second for the follow-up) created with the Open Clinica programme, version 3.14 (Copyright © OpenClinica LLC and collaborators, Waltham, MA, USA). Training sessions for data collection were held by the coordinating researcher of the study, and the quality control process included the review of at least 20% of the data of the main variables of the study to verify their agreement with the source document. If necessary, retraining and supervision sessions were held.

In the baseline assessment, sociodemographic, comorbidity, previous pharmacological treatments, and clinical presentation were collected from the emergency assessment data. The data of comorbidity and previous pharmacological treatments were collected after reviewing all the medical reports available in the computerized clinical history. We recorded the data categorically (yes/no) from a predetermined list prepared by the researchers (Table 1).

The clinical presentation variables were collected from the emergency department medical report and included symptoms and signs (categorically recorded from a predetermined list), oxygen saturation, pulmonary radiological involvement (number of affected lung quadrants, range 0-4), and the level of C-reactive protein (CRP) (hereinafter “emergency CRP”).

During each day of follow-up, the following variables were collected: hospital discharge, oxygenation system (nasal cannulas, mask, non-rebreather mask, noninvasive mechanical ventilation, orotracheal intubation), and death. For the present study, the laboratory parameters of the first day of hospitalization were also considered, which were extracted automatically by the Department of Informatics to avoid manual registration errors.

The variables considered potentially predictive were those collected in the baseline assessment and the laboratory parameters of the first day of hospitalization. The outcome variables were two: mortality and severe disease, which were verified every day of follow-up. Severe disease was defined as the need for oxygen therapy with a reservoir mask, mechanical ventilation (invasive or noninvasive), or high-flow nasal cannulas.
Regarding the predictor–outcome variable association, age and sex were considered a priori as potential confounding variables and/or effect modifiers of all other variables evaluated.

The data collection notebooks with the complete lists of variables are available in supplementary material 1 and 2.

**Statistical analysis**

For the analysis of the prognostic factors of death and severe disease, the potential predictor variables were grouped into four blocks: age–sex–comorbidity (block 1); previous pharmacological treatment (block 2); variables of clinical presentation, including pulmonary radiological involvement and CRP in the emergency room (block 3); and variables of laboratory parameters (block 4).

Within each block and for each outcome variable, a bivariate analysis was performed with each predictor variable (chi-squared or Fisher’s test for categorical variables, the T-test or Mann-Whitney test for quantitative variables), and a multivariate model was built using logistic regression, except for block 3 (in this block, it was considered more relevant to evaluate the individual predictive capacity of each parameter).

In the bivariate analysis and given the multiplicity of analyses performed, the statistical significance was adjusted by the false discovery rate (FDR) method [13].

In all the planned multivariate models, age and sex were included, given their status as potential confounding variables. The variables with significant associations (unadjusted p<0.05) found in the bivariate analysis were preselected for the models. As the primary objective of the identification of the prognostic factors with high associative strength, the least absolute shrinkage and selection operator (LASSO) method was used for the final selection of the variables to be included in the models. The LASSO method [14] is not based on p-values (which could induce the inclusion of superfluous clinical variables in the final model) but on a modification of the minimum quadratic estimation. Its objective is to select a smaller subset of explanatory variables (but with greater strength of association) with which to finally adjust the model without significantly losing any explanatory quality of the model. This procedure is considered superior to eliminating the predictor variables according to p-value. Variables with more than 30% missing values were excluded from the multivariate models, as were those with 15 or fewer individuals with the evaluated condition. Finally, based on the results of the bivariate analysis and to avoid collinearity, creatinine was excluded from the models when it coincided in the preselection with the urea variable.

Quantitative variables were not categorized. The laboratory parameters were transformed logarithmically to improve their fit to a normal distribution and were scaled to allow a comparison of their odds ratios (ORs).
Regarding the missing data, in case there were no laboratory parameters from the first day of hospitalization, these variables were imputed from their values of the second day of hospitalization if the latter were available. No missing data of other variables were imputed.

R version 3.6.1 (R Project for Statistical Computing) and IBM SPSS version 26 were used.

Results

During the recruitment period, 464 people (113 aged 80 or older) were hospitalized for suspected infection with COVID-19, of whom 418 had respiratory infection with a positive RT-PCR test for SARS-CoV-2. Of this last group, 89 people (21%) were aged 80 or more years. Additionally, 14 patients aged 80 or older identified after a second review of the hospitalization censuses were included, so 103 oldest-old people were included in the end.

The baseline assessment data are shown in Table 1. The mean age was 86.75 years (standard deviation [SD] 4.65; maximum age 99 years). Sixty-one patients (59.2%) were female, and 63 (61.2%) came from a nursing home (institutionalized). The most frequent symptoms of clinical presentation were fever (68.9%), dyspnoea (60.2%), and cough (39.8%).

All patients were followed up until discharge or death. The median follow-up was 6.0 days (interquartile range [IQR] 8 days). Fifty-nine patients (57.3%) had severe disease, and 59 patients died, with both events occurring in 43 patients. In 16 patients who died (1.1 out of every four patients who died), no criteria for severe disease were previously detected. In order to exclude medical indication for exclusive palliative care including palliative sedation as cause for not detecting criteria of severe disease, we review individually these cases and only two patients with medical indication for exclusive palliative care were detected.

The results of the bivariate analysis are shown in Table 2. Significant predictor variables (unadjusted p-value) were found for both outcome variables only in the blocks of clinical presentation variables (dyspnoea, radiological involvement, and oxygen saturation) and of laboratory parameters (aspartate aminotransferase [AST], lactate dehydrogenase [LDH], and CRP on admission), although out of all of them, only oxygen saturation survived the adjustment of multiple tests (FDR method). The urea and sodium parameters were significantly associated with mortality.

The results of the multivariate models are shown in Table 3. By the criterion of more than 30% missing data or fewer than 16 positive individuals with the evaluated parameter, the variables of stroke, psychiatric disease, emergency CRP, AST, alanine aminotransferase (ALT), and ferritin were excluded from the severe disease models; and the variables AST and “other heart disease” were excluded from the mortality models. With respect to the outcome severe disease, the variable female sex (OR 0.31, 95% CI 0.13-0.73, p 0.0074) was significantly associated with it in block 1, as was serum LDH (OR 2.55, 95% CI 1.21-5.37, p 0.0139) in block 4. Regarding the mortality outcome, only serum sodium (block 4) was significantly associated with it (OR 3.12, 95% CI 1.18-8.26, p 0.0222). Given this last result, we built a
model including laboratory parameters and oxygen saturation. In this model, serum sodium continued to be associated with higher mortality (OR 2.60, 95% CI 1.05-6.44, p 0.0394).

**Discussion/conclusion**

**Main results**

The most frequent symptoms of clinical presentation were fever, dyspnoea, and cough; hospital mortality was quite high; male sex and serum LDH level were predictors of severe disease; and serum sodium concentration was predictive of mortality.

**Clinical presentation**

Although the most frequent symptoms were the same as in the hospitalized adult population [12,15,16], they were less frequent than has been reported in this population (especially cough), even though the diagnosis of respiratory infection was an inclusion criterion in our study. On the other hand, confusion stands out as a symptom present in 11% of our sample. Gutiérrez-Rodríguez et al. and Annweiler et al. [11,17] reported frequencies similar to ours in the subgroup of patients 80 years or older. These findings are in line with those observed in the majority of diseases of this population (including infections), in which less symptomatic or atypical presentations are more frequently observed [3–5]. This reinforces the need for a lower suspicion threshold in this population, especially when evaluated in an emergency department.

A low frequency of non-respiratory symptoms was observed. However, given the absence of a systematic search for these symptoms, we cannot exclude an information bias whereby patients who reported respiratory symptoms at the beginning of the evaluation were not also asked about non-respiratory symptoms, resulting in undetected symptoms.

**Predictors of severe disease and mortality**

Age, unlike in the younger population [2,6,18,19], did not bring an added risk in any of the models built here, and male sex was a predictor of severe disease but not mortality. The trials by Gutiérrez-Rodríguez et al.[11] and Covino et al.[10] did not find that age or sex were predictors of mortality either. However, Ramos-Rincon et al.[9] reported age and male sex as predictors of mortality from a multicentre cohort of 2772 very old hospitalized patients so we cannot rule out a lack of statistical power of our sample in these results.

Unlike laboratory parameters and those related to emergency assessment (which were associated with worse prognosis), no chronic disease or previous pharmacological treatment was associated with worse or better outcomes. Previous treatments have not been evaluated as prognostic factors in the before
mentioned trials[9–11] so we cannot compare our results with them. In a younger cohort, Mostaza et al. [20], in people older than 75 years, did find a better prognosis in patients who previously took renin-angiotensin-aldosterone system antagonists. Regarding previous chronic diseases, our results are similar to the study by Ramos-Rincon et al.[9]; however, Covino et al.[10] reported severe dementia as an independent risk factor for death, although age, since it was not apparently included in their multivariate analysis, cannot be ruled out as a confounding factor.

LDH was the only predictor of severe disease among laboratory parameters. We have not found studies that evaluated the factors associated with this result in the older or oldest-old population. In adult population studies, LDH is one of the most powerful predictors of severe disease among laboratory parameters [21–24]. Thus, in the meta-analysis of Zhang et al. [23], LDH was the only predictive laboratory parameter for both adult respiratory distress syndrome and indication for Intensive Care Unit (ICU) admission. LDH is present in body tissues and is released from damaged cells [25,26], increases lactate production [27], and is a good predictor of lung injury [25].

Serum sodium was a predictor of mortality in our sample. Of the aforementioned studies, Gutiérrez-Rodríguez et al. [11] did not find a significant association in their bivariate analysis, and Ramos-Rincon et al.[9] and Covino et al.[10] did not include this parameter in their reports. Below, we propose a hypothesis for this result.

Among the laboratory parameters, it stands out that the predictors associated with worse prognosis were different for severe disease and mortality, although both outcome variables are closely related. We highlight the fact that 1.1 out of every four people who died did not previously present any criteria of severe disease. Given the definition of this in our study based on strict respiratory criteria, we hypothesize that some of the patients could have died from complications in other body systems (cardiovascular, thrombotic, metabolic, and renal complications have been described [28]) and not so much from severe respiratory involvement. In this sense, serum sodium (a marker of metabolic alteration or renal function) would predominate as a predictor of mortality and not as much of severe respiratory disease. That the association of this parameter with mortality was maintained despite adjusting the model for oxygen saturation reinforces our hypothesis.

In-hospital mortality

Although the highest lethality of COVID-19 is seen in the older population, especially among the hospitalized population, the hospital mortality found in our sample was higher than that of other hospital series of oldest-old populations in Spain (35-47%). We highlight the high proportion of institutionalized patients in our sample (61%), reflecting a population with greater clinical fragility and therefore with less ability to respond to an organic stressor. Thus, the series reported by Gutiérrez-Rodríguez et al. [11] had a mortality (41%) and a proportion of institutionalized patients (70%) more similar to those of our sample than those reported by Mostaza et al. (mortality 35% and proportion of institutionalized 23%) [20]. In neighbouring countries, Zerah et al. (France) [29] reported a lower lethality (31%) in a cohort of 821
hospitalized patients aged 70 or older, although with a proportion of institutionalized patients much lower than our sample (29%).

**External validity**

Regarding the extrapolation or comparison of our results with the results in other samples, it is important to consider, in addition to the high mortality and high proportion of institutionalized patients, that our patients were managed in secondary referral centres, so our results cannot be extrapolated to populations treated on an outpatient basis or in centres of maximum complexity (tertiary), such as patients undergoing organ transplants.

**Limitations**

The sample size of our study does not allow us to take the results as conclusive. Some laboratory parameters (AST, ALT, ferritin, and creatinine), despite having significant associations with some of the outcome variables in the bivariate analysis, could not be included in the multivariate models due to significant data loss.

Most likely, some COVID-19 patients will already be admitted with severe disease criteria. In these cases, the variables of clinical presentation and laboratory parameters could not be confirmed as predictors since no temporal relationship could be assured. However, the variables of chronic diseases and previous treatments would continue to be valid in these patients. Finally, we were unable to evaluate variables of previous functional status, a variable of known prognostic association in most diseases in this population, including COVID-19 [29,30].

In conclusion, the symptoms of clinical presentation typical of respiratory infection by SARS-CoV-2 (fever, dyspnoea, and cough) are less frequent in the oldest-old population, male sex and LDH level are predictors of severe disease, and serum sodium is associated with mortality.

**Declarations**

**Acknowledgement (optional)**

This research was conducted by the COVID-19 research group of CSAPG (led by Alejandro Rodríguez-Molinero; e-mail: rodriguez.molinero@gmail.com), which include, in addition to the authors of this paper, Alberti Casas, Anna PhD, MD; Borrego Ruiz, Manel BS; Campo Pisa, Pedro L; Fenollosa Artés, Andreu MD; Hernandez Martinez, Lourdes MD; Hidalgo García, Antonio MD; Milà Ràfols, Núria RN; Molina Hinojosa, José C MD; Monaco, Ernesto E MD; Peramiquel Fonollosa, Laura MD; Pisani Zambrano, Italo G. MD; Rives, Juan P. MD; Sabria Bach, Enric MD; Sanchez Rodriguez, Yris M. MD; Segura Martin, Maria del Mar RN; Venturini Cabanellas, Florencia I. MD; Vidal Meler, Natalia MD; Macho Pérez, Oscar MD; López, Gabriela F. MD; Robles Portillo, María Teresa MD; Dapena Díaz, María Dolores MD; Martínez, Sergi MD,
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**Statement of Ethics**

The present study has been performed in accordance with the Declaration of Helsinki and it was approved by the Research Ethics Committee of the Hospital Universitari de Bellvitge, (act 12/20, PR 252/20, date 25 June 2020), which approved the study without the need for the informed consent of the patients given the observational nature of the study and the anonymous nature of the data collected.

**Conflict of Interest Statement**

The authors have no conflicts of interest to declare.

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**Author Contributions**

César Gálvez-Barrón and Marta Arroyo-Huidobro analysed and interpreted the data, and wrote the manuscript.

Alejandro Rodríguez-Molinero designed the trial, and analysed and interpreted the data.

Antonio Miñarro analysed and interpreted the data.

Gemma Añaños, Antonio, Chamero, Mireia Martín, Clara Gris, Jose L Avalos, Anna M Capielo, Ester Ventosa, and Gemma Tremosa collected and analysed the data.

All authors read and approved the final manuscript.

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Tables

Table 1. Baseline assessment of the patients included in the study.
| Variables                      | Total | N (%)   |
|-------------------------------|-------|---------|
| **BLOCK 1. PERSONAL BACKGROUND** |       |         |
| **Sociodemographic**          |       |         |
| Female sex                    | 103   | 61 (59.2) |
| Age (SD)                      | 103   | 86.75 (4.65) |
| Institutionalized             | 103   | 63 (61.2) |
| **Autoimmune**                |       |         |
| Rheumatoid arthritis          | 103   | 0       |
| SLE                           | 103   | 0       |
| Spondyloarthropathies         | 103   | 0       |
| Scleroderma                   | 103   | 0       |
| Psoriasis                     | 103   | 0       |
| Other autoimmune disease      | 103   | 7 (6.8) |
| **Renal**                     |       |         |
| Chronic kidney failure        | 103   | 34 (33.0) |
| Peritoneal dialysis           | 103   | 0       |
| Haemodialysis                 | 103   | 1 (1.0) |
| **Cardiovascular**            |       |         |
| High blood pressure           | 103   | 84 (81.6) |
| Diabetes                      | 103   | 35 (34.0) |
| Dyslipidaemia                 | 103   | 42 (40.8) |
| Obesity                       | 103   | 13 (12.6) |
| Smoking                       | 103   | 5 (4.9)  |
| Alcohol drinking              | 103   | 1 (1.0)  |
| Heart failure                 | 103   | 17 (16.5) |
| Atrial fibrillation           | 103   | 24 (23.3) |
| Ischaemic heart disease       | 103   | 16 (15.5) |
| Other arterial ischaemia      | 103   | 2 (1.9)  |
| Aortic valve disease          | 103   | 8 (7.8)  |
| Mitral valve disease          | 103   | 7 (6.8)  |
| Disease                                | Count | Percentage |
|----------------------------------------|-------|------------|
| Prosthetic cardiac valve               | 103   | 0          |
| Other heart disease                    | 103   | 6 (5.8)    |
| Pacemaker carrier                      | 103   | 4 (3.9)    |
| Stroke                                 | 103   | 13 (12.6)  |
| Pulmonary hypertension                 | 103   | 2 (1.9)    |
| **Psychiatric**                        |       |            |
| Depression                             | 103   | 25 (24.3)  |
| Schizophrenia                          | 103   | 1 (1.0)    |
| Other psychiatric diseases             | 103   | 10 (9.7)   |
| **Neurodegenerative diseases**         |       |            |
| Dementia                               | 103   | 36 (35.0)  |
| Parkinson                              | 103   | 2 (1.9)    |
| Multiple sclerosis                     | 103   | 0          |
| Other neurodegenerative diseases       | 103   | 4 (3.9)    |
| **Digestive**                          |       |            |
| Gastropathy                            | 103   | 7 (6.8)    |
| Inflammatory bowel disease             | 103   | 4 (3.9)    |
| Cirrhosis                              | 103   | 0          |
| Celiac disease                         | 103   | 0          |
| Other liver disease                    | 103   | 4 (3.9)    |
| **Respiratory**                        |       |            |
| Asthma                                 | 103   | 3 (2.9)    |
| COPD                                   | 103   | 16 (15.5)  |
| Cystic fibrosis                        | 103   | 0          |
| Other pneumopathy                      | 103   | 4 (3.9)    |
| **Other**                              |       |            |
| Thyroid disease                        | 103   | 13 (12.6)  |
| HIV/AIDS                               | 103   | 0          |
| Transplant                             | 103   | 0          |
| Immunosuppression due to other causes  | 103   | 0          |
### Chronic anaemia

| Condition          | Count | Percentage |
|--------------------|-------|------------|
| HCV                | 103   | 0          |

### Block 2. Pharmacological Treatments

#### Haematological
- **Antiplatelet agents**: 103 (32.0)
- **Anticoagulants**: 103 (16.5)

#### Analgesics and corticosteroids
- **Paracetamol**: 103 (41.7)
- **NSAIDs**: 103 (7.8)
- **Opioids**: 103 (12.6)
- **Systemic corticosteroids**: 103 (4.9)

#### Antidiabetic
- **Insulin**: 103 (9.7)
- **Metformin**: 103 (19.4)
- **Other oral antidiabetic drugs**: 103 (8.7)

#### Cardiovascular
- **Lipid-lowering drugs**: 103 (25.2)
- **Diuretics**: 103 (44.7)
- **Beta blockers**: 103 (16.5)
- **ACE inhibitors**: 103 (29.1)
- **ARA 2**: 103 (20.4)
- **Other antihypertensives**: 103 (30.1)

#### Respiratory
- **Inhaled anticholinergics**: 103 (11.7)
- **β₂ inhaled agonists**: 103 (13.6)
- **Inhaled corticosteroids**: 103 (9.7)
- **Other inhalers**: 103 (1.9)
- **Home oxygen therapy**: 103 (3.9)

#### CNS
| Medication Class                              | Count | Percentage |
|----------------------------------------------|-------|------------|
| Sedatives                                    | 103   | 32 (31.1)  |
| Antidepressants                              | 103   | 41 (39.8)  |
| Antipsychotics                               | 103   | 30 (29.1)  |
| Antiepileptics                               | 103   | 4 (3.9)    |
| Antiparkinsonians                            | 103   | 4 (3.9)    |
| Other drugs with effect on CNS               | 103   | 14 (13.6)  |

**Other therapies**

| Therapy                        | Count | Percentage |
|--------------------------------|-------|------------|
| Antacids                       | 103   | 51 (49.5)  |
| Cytotoxic/chemotherapy         | 103   | 0          |
| Drugs with immune action       | 103   | 0          |
| Antihistamines                 | 103   | 1 (1.0)    |

**BLOCK 3. CLINICAL PRESENTATION**

| Symptom                        | Count | Percentage |
|--------------------------------|-------|------------|
| Fever                          | 103   | 71 (68.9)  |
| Dyspnoea                       | 103   | 62 (60.2)  |
| Cough                          | 103   | 41 (39.8)  |
| Diarrhoea                      | 103   | 16 (15.5)  |
| Arthromyalgia                  | 103   | 6 (5.8)    |
| Asthenia                       | 103   | 22 (21.4)  |
| Anosmia                        | 103   | 0          |
| Altered taste                  | 103   | 0          |
| Skin lesions                   | 103   | 0          |
| Headache                       | 103   | 0          |
| Confusion                      | 103   | 12 (11.7)  |
| Psychomotor agitation (%)      | 103   | 3 (2.9)    |
| Chest X-ray (affected quadrants)| 103   |            |
| 0                              |       | 12 (12.6)  |
| 1                              |       | 15 (15.8)  |
| 2                              |       | 36 (37.9)  |
| 3                              |       | 15 (15.8)  |
| 4                              |       | 17 (17.9)  |
| Parameter                                      | n  | Mean (SD)         |
|-----------------------------------------------|----|-------------------|
| CRP in emergencies, mean (SD)                 | 34 | 151.03 (110.72)   |
| Basal oxygen saturation (Emergency), mean (SD)| 93 | 86.82 (10.56)     |
| **BLOCK 4. LABORATORY PARAMETERS (day 1 of admission)** |    |                   |
| Haemoglobin (g/dL)                            | 87 | 12.53 (2.21)      |
| Platelets (10^9/L)                            | 85 | 232.79 (117.17)   |
| Neutrophils (10^9/L)                          | 82 | 7.27 (4.38)       |
| Lymphocytes (10^9/L)                          | 87 | 1.16 (0.89)       |
| Eosinophils (10^9/L)                          | 87 | 0.32 (0.63)       |
| Prothrombin time (INR)                        | 84 | 1.28 (0.48)       |
| D-dimer (ng/ml)                               | 71 | 2842.82 (3468.59) |
| Fibrinogen                                    | 15 | 614.67 (242.51)   |
| Glucose (mg/dL)                               | 87 | 149.44 (64.36)    |
| Sodium (mEq/L)                                | 87 | 141.64 (8.25)     |
| Creatinine (mg/dL)                            | 87 | 1.49 (0.92)       |
| Urea (mg/dL)                                  | 87 | 78.36 (54.11)     |
| Alkaline phosphatase (IU/L)                   | 50 | 73.99 (30.42)     |
| AST (IU/L)                                    | 60 | 44.85 (44.22)     |
| ALT (IU/L)                                    | 66 | 28.15 (14.57)     |
| GGTP (IU/L)                                   | 53 | 50.57 (27.47)     |
| Total bilirubin (mg/dL)                       | 70 | 0.66 (0.49)       |
| LDH (U/L)                                     | 73 | 325.01 (131.48)   |
| CRP at admission (mg/L)                       | 80 | 13.37 (10.83)     |
| Ferritin (µg/L)                               | 48 | 518.44 (491.55)   |
| Procalcitonin (ng/mL)                         | 30 | 0.80 (1.34)       |
| Lactate (mmol/L)                              | 20 | 2.14 (1.79)       |
| Arterial oxygen (mmHg)                        | 61 | 73.61 (30.30)     |
| Carbon dioxide (mmHg)                         | 61 | 24.45 (4.32)      |
| Serum bicarbonate (mmol/L)                    | 71 | 24.79 (3.38)      |
| pH                                           | 61 | 7.46 (0.05)       |
Table 2. Bivariate analysis of the variables of severe disease and mortality.
| VARIABLES | SEVERE DISEASE | MORTALITY |
|-----------|---------------|-----------|
|           | yes, n (%)/no, n (%) | OR (95% CI)* or mean dif. (95% CI) | p-value | p_adj | yes, n (%)/no, n (%) | OR (95% CI)* or mean dif. (95% CI) | p-value | p_adj |
|           |               | **OR (95% CI)*** or **mean dif. (95% CI)** | **p - value** | **p_adj** |           | **OR (95% CI)*** or **mean dif. (95% CI)** | **p - value** | **p_adj** |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
|           |               | p - value | p_adj | p - value | p_adj |
### BLOCK 2.
**PHARMACOLOGICAL TREATMENTS**

#### Haematological

| Condition                  | Cases | Controls | OR (95% CI) | p-value | Corrected OR | Corrected p-value |
|----------------------------|-------|----------|-------------|---------|--------------|-------------------|
| **Atrial fibrillation**    | 15 (63)/44 (56) | 1.32 (0.52 - 3.51) | 0.64 | 1.00 | 16 (67)/43 (54) | 1.65 (0.64 - 4.55) | 0.35 | 0.97 |
| **Psychiatric**            |       |          |             |         |              |                   |
| Depression                 | 14 (56)/45 (58) | 0.93 (0.37 - 2.37) | 1.00 | 1.00 | 13 (52)/46 (59) | 0.76 (0.30 - 1.90) | 0.64 | 1.00 |
| Schizophrenia              | 0/59 (58)  | 0.00 (0.00 - 6.13) | 0.43 | 0.96 | 0/59 (58)     | 0.00 (0.01 - 6.13) | 0.43 | 1.00 |
| Other psychiatric diseases | 2 (20)/57 (61) | 0.17 (0.02 - 0.74) | 0.02 | 0.23 | 3 (30)/56 (60) | 0.29 (0.06 - 1.16) | 0.09 | 0.62 |
| **Neurodegenerative diseases** |       |          |             |         |              |                   |
| Dementia                   | 19 (53)/40 (60) | 0.76 (0.33 - 1.73) | 0.54 | 1.00 | 24 (67)/35 (52) | 1.81 (0.78 - 4.34) | 0.21 | 0.97 |
| Parkinson’s disease        | 1 (50)/58 (57) | 0.74 (0.02 - 29.56) | 1.00 | 1.00 | 1 (50)/58 (57) | 0.74 (0.02 - 29.56) | 1.00 | 1.00 |
| Neurodegenerative disease | 1 (25)/58 (59) | 0.26 (0.01 - 2.32) | 0.31 | 0.89 | 2 (50)/57 (58) | 0.74 (0.07 - 7.34) | 1.00 | 1.00 |
| **Digestive**              |       |          |             |         |              |                   |
| Gastropathy                | 5 (71)/54 (56) | 1.86 (0.36 - 14.99) | 0.70 | 1.00 | 4 (57)/55 (57) | 0.98 (0.20 - 5.59) | 1.00 | 1.00 |
| Inflammatory bowel disease | 2 (50)/57 (58) | 0.74 (0.07 - 7.34) | 1.00 | 1.00 | 1 (25)/58 (59) | 0.26 (0.01 - 2.32) | 0.31 | 0.97 |
| Other liver disease        | 4 (100)/55 (56) | 3.14 (0.38 - 137.63) | 0.13 | 0.69 | 3 (75)/56 (57) | 2.11 (0.24 - 61.97) | 0.63 | 1.00 |
| **Respiratory**            |       |          |             |         |              |                   |
| Asthma                     | 2 (67)/57 (57) | 1.42 (0.11 - 45.48) | 1.00 | 1.00 | 1 (33)/58 (58) | 0.39 (0.01 - 4.94) | 0.57 | 1.00 |
| COPD                       | 10 (63)/49 (56) | 1.28 (0.43 - 4.14) | 0.79 | 1.00 | 9 (56)/50 (58) | 0.95 (0.32 - 2.93) | 1.00 | 1.00 |
| Other lung disease         | 3 (75)/56 (57) | 2.11 (0.24 - 61.97) | 0.63 | 1.00 | 2 (50)/57 (58) | 0.74 (0.07 - 7.34) | 1.00 | 1.00 |
| **Other**                  |       |          |             |         |              |                   |
| Thyroid disease            | 6 (46)/53 (59) | 0.60 (0.18 - 2.00) | 0.55 | 1.00 | 5 (39)/54 (60) | 0.42 (0.12 - 1.40) | 0.23 | 0.97 |
| Chronic anaemia            | 6 (50)/53 (58) | 0.72 (0.20 - 2.53) | 0.76 | 1.00 | 7 (58)/52 (57) | 1.04 (0.30 - 3.87) | 1.00 | 1.00 |

#### Painkillers

| Condition                  | Cases | Controls | OR (95% CI) | p-value | Corrected OR | Corrected p-value |
|----------------------------|-------|----------|-------------|---------|--------------|-------------------|
| **Atrial fibrillation**    |       |          |             |         |              |                   |
| Depression                 |       |          |             |         |              |                   |
| Schizophrenia              |       |          |             |         |              |                   |
| Other psychiatric diseases |       |          |             |         |              |                   |
| **Neurodegenerative diseases** |       |          |             |         |              |                   |
| Dementia                   |       |          |             |         |              |                   |
| Parkinson’s disease        |       |          |             |         |              |                   |
| Neurodegenerative disease |       |          |             |         |              |                   |
| **Digestive**              |       |          |             |         |              |                   |
| Gastropathy                |       |          |             |         |              |                   |
| Inflammatory bowel disease |       |          |             |         |              |                   |
| Other liver disease        |       |          |             |         |              |                   |
| **Respiratory**            |       |          |             |         |              |                   |
| Asthma                     |       |          |             |         |              |                   |
| COPD                       |       |          |             |         |              |                   |
| Other lung disease         |       |          |             |         |              |                   |
| **Other**                  |       |          |             |         |              |                   |
| Thyroid disease            |       |          |             |         |              |                   |
| Chronic anaemia            |       |          |             |         |              |                   |
| Drug Class                | Cases (Percentage) | Prevalence Ratio | OR (95% CI)  | Occurrence Rate | p-Value | OR (95% CI)  | p-Value |
|--------------------------|--------------------|------------------|--------------|----------------|---------|--------------|---------|
| Paracetamol              | 23 (54)/36 (60)    | 0.77 (0.35 - 1.71) | 0.55         | 1.00           | 27 (63)/32 (53) | 1.47 (0.66 - 3.33) | 0.42 | 1.00 |
| NSAIDs                   | 2 (25)/57 (60)     | 0.24 (0.03 - 1.13) | 0.07         | 0.47           | 3 (38)/56 (59) | 0.43 (0.08 - 1.93) | 0.28 | 0.97 |
| Opioids                  | 7 (54)/52 (58)     | 0.85 (0.26 - 2.91) | 1.00         | 1.00           | 7 (54)/52 (58) | 0.85 (0.26 - 2.91) | 1.00 | 1.00 |
| Systemic corticosteroids | 5 (100)/54 (55)    | 4.00 (0.48 - 166.87) | 0.07         | 0.47           | 3 (60)/56 (57) | 1.10 (0.16 - 9.81) | 1.00 | 1.00 |
| Antihistamines           | 1 (100)/58 (57)    | 0.75 (0.09 - 57.36) | 1.00         | 1.00           | 1 (100)/58 (57) | 0.75 (0.09 - 57.36) | 1.00 | 1.00 |
| Antidiabetic             |                    |                  |              |                |                     |                      |       |       |
| Insulin                  | 5 (50)/54 (58)     | 0.72 (0.18 - 2.87) | 0.74         | 1.00           | 4 (40)/55 (59) | 0.47 (0.11 - 1.81) | 0.32 | 0.97 |
| Metformin                | 13 (65)/46 (55)    | 1.48 (0.54 - 4.35) | 0.46         | 1.00           | 13 (65)/46 (55) | 1.48 (0.54 - 4.35) | 0.46 | 1.00 |
| Other oral antidiabetic drugs | 7 (78)/52 (55) | 2.67 (0.59 - 20.59) | 0.29         | 0.89           | 5 (56)/54 (57) | 0.92 (0.22 - 4.10) | 1.00 | 1.00 |
| Cardiovascular           |                    |                  |              |                |                     |                      |       |       |
| Lipid-lowering drugs     | 17 (65)/42 (55)    | 1.56 (0.62 - 4.11) | 0.37         | 0.96           | 11 (42)/48 (62) | 0.45 (0.18 - 1.11) | 0.11 | 0.64 |
| Diuretics                | 24 (52)/35 (61)    | 0.69 (0.31 - 1.52) | 0.42         | 0.96           | 27 (59)/32 (56) | 1.11 (0.50 - 2.46) | 0.84 | 1.00 |
| Beta blockers            | 7 (41)/52 (61)     | 0.46 (0.15 - 1.34) | 0.18         | 0.80           | 6 (35)/53 (62) | 0.35 (0.11 - 1.01) | 0.06 | 0.48 |
| ACE inhibitors           | 19 (63)/40 (55)    | 1.41 (0.59 - 3.50) | 0.51         | 1.00           | 20 (67)/39 (53) | 1.72 (0.72 - 4.36) | 0.27 | 0.97 |
| ARA2                     | 15 (71)/44 (54)    | 2.12 (0.77 - 6.56) | 0.22         | 0.89           | 10 (48)/49 (60) | 0.62 (0.23 - 1.64) | 0.33 | 0.97 |
| Other antihypertensives  | 15 (48)/44 (61)    | 0.60 (0.25 - 1.41) | 0.28         | 0.89           | 18 (58)/41 (57) | 1.04 (0.44 - 2.50) | 1.00 | 1.00 |
| Antiarrhythmics          | 7 (78)/52 (55)     | 2.67 (0.59 - 20.59) | 0.29         | 0.89           | 7 (78)/52 (55) | 2.67 (0.59 - 20.50) | 0.29 | 0.97 |
| Respiratory              |                    |                  |              |                |                     |                      |       |       |
| Inhaled anticholinergics | 7 (58)/52 (57)     | 1.04 (0.30 - 3.87) | 1.00         | 1.00           | 6 (50)/53 (58) | 0.72 (0.20 - 2.53) | 0.76 | 1.00 |
| β<sub>2</sub> inhaled agonists | 9 (64)/50 (56) | 1.38 (0.43 - 4.94) | 0.77         | 1.00           | 7 (50)/52 (58) | 0.71 (0.22 - 2.30) | 0.57 | 1.00 |
| Inhaled corticosteroids  | 7 (70)/52 (56)     | 1.78 (0.45 - 9.18) | 0.51         | 1.00           | 6 (60)/53 (57) | 1.12 (0.29 - 4.82) | 1.00 | 1.00 |
| Other inhalers           | 1 (50)/58 (57)     | 0.74 (0.02 - 29.56) | 1.00         | 1.00           | 1 (50)/58 (57) | 0.74 (0.02 - 29.56) | 1.00 | 1.00 |
| CNS                      |                    |                  |              |                |                     |                      |       |       |
| Sedatives                | 21 (66)/38 (54)    | 1.64 (0.70 - 4.04) | 0.29         | 0.89           | 17 (53)/42 (59) | 0.78 (0.33 - 1.84) | 0.67 | 1.00 |
| Antidepressants          | 24 (59)/35 (57)    | 1.09 (0.49 - 2.45) | 1.00         | 1.00           | 22 (54)/37 (60) | 0.78 (0.35 - 1.75) | 0.68 | 1.00 |
| Antipsychotics           | 20 (67)/39 (53)    | 1.72 (0.72 - 4.36) | 0.27         | 0.89           | 20 (67)/39 (53) | 1.72 (0.72 - 4.36) | 0.27 | 0.97 |
| Antiepileptics           | 3 (75)/56 (57)     | 2.11 (0.24 - 61.97) | 0.63         | 1.00           | 3 (75)/56 (57) | 2.11 (0.24 - 61.97) | 0.63 | 1.00 |
Antiparkinsonians 3 (75)/56 (57) 2.11 (0.24 - 61.97) 0.63 1.00 2 (50)/57 (58) 0.74 (0.07 - 7.34) 1.00 1.00

Other drugs with effect on the CNS 5 (36)/54 (61) 0.37 (0.10 - 1.18) 0.09 0.54 6 (43)/53 (60) 0.52 (0.15 - 1.64) 0.26 0.97

Other therapies

Antacids 31 (61)/28 (54) 1.32 (0.60 - 2.93) 0.55 1.00 29 (57)/30 (58) 0.97 (0.44 - 2.13) 1.00 1.00

BLOCK 3. CLINICAL PRESENTATION

Dyspnoea 42 (68)/17 (42) 2.92 (1.30 - 6.78) 0.01 0.21 42 (68)/17 (42) 2.92 (1.30 - 6.78) 0.01 0.21

Cough 23 (56)/36 (58) 0.92 (0.41 - 2.07) 1.00 1.00 17 (42)/42 (68) 0.34 (0.15 - 0.77) 0.01 0.21

Fever 45 (63)/14 (44) 2.20 (0.94 - 5.26) 0.09 0.53 42 (59)/17 (53) 1.28 (0.54 - 2.99) 0.67 1.00

Diarrhoea 8 (50)/51 (59) 0.71 (0.24 - 2.13) 0.58 1.00 8 (50)/51 (59) 0.71 (0.24 - 2.13) 0.59 1.00

Arthromyalgia 3 (50)/56 (58) 0.73 (0.12 - 4.47) 1.00 1.00 1 (17)/58 (60) 0.15 (0.01 - 1.03) 0.08 0.57

Asthenia 10 (46)/49 (61) 0.55 (0.21 - 1.43) 0.23 0.89 6 (27)/53 (65) 0.20 (0.07 - 0.56) 0.003 0.09

Confusion 5 (42)/54 (59) 0.50 (0.13 - 1.71) 0.35 0.96 9 (75)/50 (55) 2.37 (0.64 - 11.82) 0.23 0.97

Psychomotor agitation 1 (33)/58 (59) 0.39 (0.01 - 4.94) 0.57 1.00 3 (100)/56 (56) 2.32 (0.28 - 109.54) 0.26 0.97

X-ray, affected quadrants 2.42 (n=55)/1.68 (n=40) 0.74 0.004 0.10 2.33 (1.2)/1.80 (1.3) 0.039 0.36

CRP in the emergency department 187.84 (n=19)/104.40 (n=15) 83.44 0.027 0.30 175.8 (118.4)/105.6 (80.7) 0.08 0.57

Basal oxygen saturation (emergency department) 83.35 (n=55)/91.84 (n=38) -8.49 0.0001 0.006 83.7 (11.3)/90.9 (7.9) 0.001 0.036

BLOCK 4. LABORATORY PARAMETERS**

| Parameter                  | Mean (SD)       | Mean dif. (95% CI)         | p-value | p_adj | Mean (SD)       | Mean dif. (95% CI)         | p-value | p_adj |
|----------------------------|-----------------|----------------------------|---------|-------|-----------------|----------------------------|---------|-------|
| Haemoglobin (g/L)          | 12.5 (2.394)/12.5 (1.943) | -0.03 (-0.99 - 0.93)       | 0.950   | 1.00  | 12.6 (2.4)/12.5 (2.0) | -0.07 (-1.03 - 0.88)       | 0.96    | 1.00  |
| Platelets (10⁹/L)          | 212.8 (98)/260.0 (135)      | 47.16 (-3.27 - 97.58)      | 0.037   | 0.35  | 227.5 (96.0)/239.6 (141.1) | 12.10 (-39.12 - 63.32)      | 0.94    | 1.00  |
| Neutrophils (10⁹/L)        | 7.2 (4.5)/7.3 (4.3)         | 0.12 (-1.84 - 2.08)        | 0.791   | 1.00  | 7.8 (5.0)/6.6 (3.4)      | -1.24 (-3.10 - 0.62)        | 0.38    | 1.00  |
| Test                                      | Reference Range | Lower Limit | Upper Limit | P Value  | Significance |
|-------------------------------------------|-----------------|-------------|-------------|----------|--------------|
| **Lymphocytes (10^9/L)**                  | 1.0 (0.7)/1.4 (1.2) | 0.44 (0.02 - 0.87) | 0.056 (0.01 - 0.76) | 0.22 (0.24) |
| **Eosinophils (10^9/L)**                  | 0.2 (0.5)/0.5 (0.8) | 0.24 (-0.05 - 0.53) | 0.0188 (0.01 - 0.34) | 0.59 (0.88) |
| **Prothrombin time, INR**                | 1.2 (0.3)/1.4 (0.7) | 0.12 (-0.13 - 0.36) | 0.554 (0.01 - 0.34) | 0.53 (1.00) |
| **D-dimer (ng/mL)**                       | 3156.4 (2895.5)/2460.6 (2145.3) | -695.79 (-2349.74 - 911.78) | 0.263 (0.01 - 0.34) | 0.55 (1.00) |
| **Fibrinogen**                           | 652.7 (259.7)/510.0 (220.5) | -142.73 (-448.44 - 162.99) | 0.544 (0.01 - 0.34) | 0.88 (1.00) |
| **Glucose (mg/dL)**                       | 157.7 (74.4)/137.1 (67.9) | -20.55 (-48.34 - 7.24) | 0.181 (0.01 - 0.34) | 0.33 (0.97) |
| **Serum sodium (mEq/L)**                 | 141.5 (8.2)/141.8 (8.0) | 0.32 (-3.28 - 3.93) | 0.865 (0.01 - 0.34) | 0.0001 (0.006) |
| **Creatinine (mg/dL)**                    | 1.54 (0.7)/1.42 (1.2) | -0.12 (-0.52 - 0.28) | 0.068 (0.01 - 0.34) | 0.005 (0.12) |
| **Urea (mg/dL)**                          | 78.7 (69.2) | -0.74 (-24.40 - 22.92) | 0.246 (0.01 - 0.34) | 0.0001 (0.006) |
| **Alkaline phosphatase (IU/L)**           | 68.0 (34.7) | 13.63 (-3.52 - 30.79) | 0.122 (0.01 - 0.34) | 0.30 (0.97) |
| **AST (IU/L)**                            | 54.3 (19.9) | -19.65 (-42.3 - 2.83) | 0.028 (0.01 - 0.34) | 0.016 (0.21) |
| **ALT (IU/L)**                            | 32.0 (10.8) | -8.31 (-15.24 - 1.38) | 0.012 (0.01 - 0.34) | 0.92 (1.00) |
| **GGTP (IU/L)**                           | 55.0 (23.7) | -9.36 (-24.45 - 5.73) | 0.400 (0.01 - 0.34) | 0.31 (0.97) |
| **Total bilirubin (mg/dL)**               | 0.6 (0.4) | 0.08 (-0.16 - 0.32) | 0.636 (0.01 - 0.34) | 0.69 (1.00) |
| **LDH (U/L)**                             | 373.8 (147.2)/262.5 (70.8) | -111.27 (-167.70 - 54.83) | 0.0001 (0.006) | 0.006 (0.12) |
| **CRP at admission (mg/L)**               | 15.8 (11.8)/10.1 (8.5) | -5.75 (-10.49 - 1.02) | 0.004 (0.01 - 0.34) | 0.019 (0.22) |
| **Ferritin (µg/L)**                       | 696.2 (291.0) | -387.82 (-642.31 - 133.33) | 0.004 (0.01 - 0.34) | 0.68 (1.00) |
| Parameter                        | Mean (SD)          | 95% CI       | p-value | p-adj       | OR (95% CI) | 95% CI       |
|---------------------------------|--------------------|--------------|---------|-------------|-------------|--------------|
| Procalcitonin (ng/mL)           | 0.8 (1.21)/0.8     | -0.01 (-1.13 - 1.10) | 0.268   | 0.89        | 0.8 (1.3)/0.7 | -0.10 (-1.13 - 0.93) |
| Lactate (mmol/L)                | 2.1 (2.2)/2.2      | 0.07 (-1.74 - 1.88) | 0.306   | 0.89        | 2.6 (2.2)/1.5 | -1.03 (-2.71 - 0.66) |
| Arterial oxygen (mmHg)          | 70.7 (34.0)/77.0   | 6.30 (-9.32 - 21.93) | 0.53    | 1.00        | 68.1 (27.7)/80.5 | 12.42 (-3.00 - 27.85) |
| Arterial carbon dioxide (mmHg)  | 24.0 (3.1)/24.9    | 0.89 (-1.34 - 3.12) | 0.81    | 1.00        | 23.7 (4.0)/25.4 | 1.70 (-0.50 - 3.91) |
| Serum bicarbonate (mmol/l)      | 24.3 (2.7)/25.3    | 1.00 (-0.73 - 2.73) | 0.51    | 1.00        | 24.2 (3.2)/25.5 | 1.24 (-0.49 - 2.97) |
| Blood pH                        | 7.45 (0.06)/7.47   | 0.01 (-0.01 - 0.04) | 0.315   | 0.89        | 7.46 (0.06)/7.46 | -0.00 (-0.03 - 0.03) |

*: in the case that any cell had a value of 0, for the calculation of the OR, a normal approximation was performed with adjustment for small samples.

**: for the laboratory parameters, the values of p and p_adj come from the bivariate analysis of the logarithmically transformed parameter

Table 3. Results of the multivariate analysis for the variables of severe disease and mortality
| Model * | Severe disease | Mortality |
|---------|----------------|------------|
|         | OR ** 95% CI    | p          | OR ** 95% CI | p          |
| Model 1: Personal history |                |            |               |            |
| Female sex | 0.31 0.13 - 0.73 | 0.007       | 0.48 0.21 - 1.10 | 0.082       |
| Model 2: Pharmacological treatments |                |            |               |            |
| Female sex | 0.31 0.13 - 0.73 | 0.007       | 0.48 0.21 - 1.10 | 0.082       |
| Model 3: Laboratory parameters |                |            |               |            |
| Female sex | 0.29 0.09 - 0.95 | 0.041       | 0.40 0.11 - 1.45 | 0.161       |
| Serum LDH | 2.55 1.21 - 5.37 | 0.014       | 1.65 0.88 - 3.10 | 0.121       |
| CRP on admission | 1.93 0.89 - 4.17 | 0.094       |               |            |
| Serum sodium |                      |            | 3.12 1.18 - 8.26 | 0.022       |
| Serum urea |                      |            | 1.49 0.66 - 3.39 | 0.339       |
| Lymphocytes |                      |            | 0.78 0.39 - 1.56 | 0.484       |
| Model 4: Laboratory parameters and oxygen saturation |                |            |               |            |
| LDH | 2.54 1.03 - 6.23 | 0.042       | 1.60 0.87 - 2.93 | 0.128       |
| CRP on admission | 2.11 0.83 - 5.38 | 0.118       |               |            |
| Basal oxygen saturation | 0.94 0.86 - 1.04 | 0.222       |               |            |
| Serum sodium |                      |            | 2.60 1.05 - 6.44 | 0.0394      |
| Serum urea |                      |            | 1.54 0.70 - 3.38 | 0.281       |

*: in each model, the variables age and sex were included, except in model 4.

**: laboratory parameters (LDH, CRP, sodium, urea, and lymphocytes) were subjected to logarithmic transformation and then scaled, so their ORs cannot be compared with those of the other variables (sex and oxygen saturation).