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Evaluation of prognostic factors for intensive care unit admission and mortality in patients hospitalised in pneumo-COVID unit at Princess Grace Hospital, Monaco

Valentin Pruvot

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UNIVERSITE CÔTE D'AZUR
ANNEE 2022



THESE D'EXERCICE DE MEDECINE
Pour l'obtention du diplôme d'État de Docteur en Médecine

**EVALUATION OF PROGNOSTIC FACTORS FOR INTENSIVE CARE
UNIT ADMISSION AND MORTALITY IN PATIENTS HOSPITALISED
IN PNEUMO-COVID UNIT AT PRINCESS GRACE HOSPITAL,
MONACO**

Présentée et soutenue le 24 février 2023,
À la faculté de Médecine de Nice

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Né le 29 juin 1992 à Blois (41)

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À ma famille et tout particulièrement ma petite mamie

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Évaluation des facteurs pronostiques d'admission en unité de soins intensifs et de mortalité des patients hospitalisés en pneumo-COVID au CHPG de Monaco

Introduction : La COVID19 est une maladie multi-systémique aboutissant tant à des formes asymptomatiques qu'à des détresses respiratoires. Ces dernières formes ont exercé une contrainte inédite sur nos systèmes de santé et ont conduit à des mesures sanitaires sans précédent. L'objectif de cette étude est de caractériser les différences associées au pronostic défavorable (transfert en unité de soins intensifs et décès) chez les malades hospitalisés pour une forme modérée en unité pneumo-COVID à Monaco.

Matériel et méthode : Cette étude monocentrique observationnelle conduite au Centre Hospitalier Princesse Grasse en Principauté de Monaco du 1^{er} septembre 2020 au 14 avril 2021 compare les caractéristiques à l'admission dans l'unité pneumo-COVID des patients évoluant secondairement vers la réanimation en excluant les LATA, et des patients décédés, en analyse univariée puis à l'aide d'une régression logistique multivariée.

Résultats : Parmi les 332 patients inclus, 76 ont été transférés en réanimation. Les facteurs prédictifs de forme sévère étaient : l'âge (p0,0063), le sexe masculin (p0,0029), l'hypertension artérielle (p0,0102), l'AOMI (p0,0318), l'atteinte parenchymateuse au scanner (p0,0025), les neutrophiles (p0,0241), les éosinophiles (p0,0406), les plaquettes (p0,0061), l'urée (p0,0120) la créatinine (p0,0274), la glycémie (p0,0012), le phosphore (p0,0067), l'ASAT (p0,0303), la CRP (p<0,001), la PCT (p<0,0001), la SpO2 aux urgences (p<0,001), la SpO2 à l'admission en unité COVID (p0,0004), la fréquence respiratoire dans le service (p0,0229) la dyspnée (p0,0004) et l'absence d'anosmie (p0,0182). En analyse multivariée le sexe masculin (p0,0056), l'éosinopénie (p0,0491) et la saturation pulsée en oxygène aux urgences (p0,0030) restent significativement associés au passage en réanimation. L'analyse multivariée des patients décédés quant à elle objective l'âge (p0,0033), les plaquettes (p0,0195), l'atteinte parenchymateuse au scanner (p0,043) et la kaliémie (p0,0181) comme facteur de risque de cette cohorte.

Discussion : Les données clinico biologiques mis en évidence sont un outil supplémentaire au clinicien pour optimiser sa prise en charge. De plus les mécanismes sous-tendus sont d'autant de piste pour la compréhension de la maladie, et l'amélioration des soins.

Summary

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Abbreviations

(by order of appearance in the Text)

| | |
|---------------------------|--|
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus 2 |
| MERS-CoV | Middle East respiratory syndrome coronavirus |
| RNA | Ribonucleic acid |
| ACE2 | Angiotensin-2-converting enzyme |
| WHO | World Health Organization |
| SpO ₂ | Oxygen pulse saturation |
| AA | Ambient air |
| RR | Respiratory rate |
| COVID19 | Coronavirus infectious disease 2019 |
| ENT | Ear, nose and throat (ORL) |
| GFR | Glomerular filtration rate |
| CKD-EPI | Chronic Kidney Disease Epidemiology collaboration |
| BMI | Body mass index |
| Ratio N/L | Neutrophil to lymphocyte ratio |
| COPD | Chronic obstructive pulmonary disease |
| CRP | C reactive protein |
| PCT | Procalcitonin |
| ASAT | Aspartate aminotransferase |
| ALAT | Alanine aminotransferase |
| CPK | Creatin phosphokinase |
| LDH | Lactate dehydrogenase |
| PT (TP) | Prothrombin time |
| IL | Interleukin |
| HbA1c | Glycated hemoglobin |
| NTproBNP | N-terminal fragment of natriuretic propeptide |
| CHPG | Princess Grace Hospital Center |
| ICU | Intensive care unit |
| DIM | Département d'information médicale |
| FB | Frédéric Berthier |
| LATA active therapies) | Limitation et arrêt des thérapeutiques actives (Limiting and stopping active therapies) |
| RT-PCR | Reverse transcription polymerase chain reaction |
| VP | Valentin Pruvot |
| GC | Gilles Chironi |

| | |
|---------|---------------------------------------|
| CT-scan | Computed tomography scanner |
| NIH | National Institutes of Health |
| BCC | Blood cell count |
| APTT | Activated partial thromboplastin time |
| GGT | Gamma glutamyl transferase |
| OR | Odds Ratio |
| SD | Standard deviation |
| PAD | Peripheral arterial disease |
| SAS | Sleep apnea syndrome |
| LTO | Long term oxygenotherapy |
| NSAID | Non steroids anti-inflammatory drugs |
| CTC | Corticosteroids |

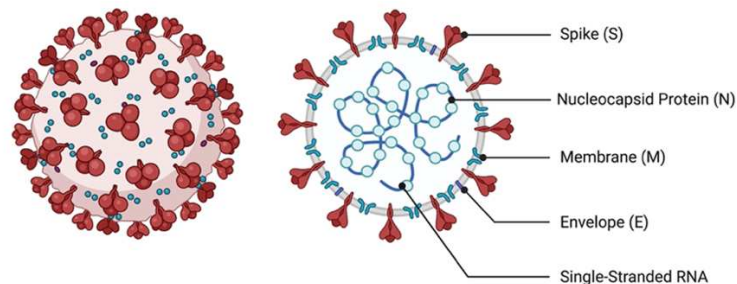
Introduction

Severe cases of a new infectious pneumonia were first reported in Wuhan, China, in December 2019. The pathogen was quickly identified and named SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2).

SARS-CoV-2 belongs to the genus of coronaviruses, a family of viruses responsible for mainly respiratory and digestive infections in mammals and birds, such as infectious feline peritonitis, chicken's infectious bronchitis or porcine epidemic diarrhea... They have in common the particularity of being highly transmissible. To date, seven coronaviruses are known to be pathogenic in humans. Three of them, of the beta genus, have been responsible for severe respiratory outbreak. SARS-CoV-1 between 2002 and 2004 in China, MERS-CoV in 2012 in the Middle East and SARS-CoV-2 since December 2019 in China, then worldwide. (1) SARS-CoV-1 and SARS-CoV-2 are closely related and originate from bats, which are very likely to serve as reservoir hosts. (2,3)

SARS-CoV-2 has a very simple structure: a single-stranded RNA and a spherical envelope composed of membrane glycoproteins, envelope proteins and surface proteins, including the SPIKE protein.

Human SARS-CoV-2 Structure



Structural elements of the virus, including the spike protein, envelope, membrane, and internal components such as the viral single-stranded RNA and nucleocapsid proteins.

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Coronaviruses use their SPIKE glycoprotein to bind to the host cellular ACE2 receptors. This binding triggers a cascade of events that leads to the fusion between the cellular and viral membranes allowing entry of the viral material into the cells. (4) The virus then hijacks the cellular machinery to replicate itself.

ACE2 receptors are highly expressed in lung, intestinal, cardiac, adipose, renal, testicular, hepatic and brain cells, making this disease polymorphic. (5,6) The disease may manifest itself

as an asymptomatic form, a moderate form (ENT infection, flu-like syndrome, fever, cough, headache, diarrhea, etc.), a severe form according to the WHO defined by the presence of fever, cough, dyspnea, and one of the following signs : RR > 30/minute, SpO₂ < 90% in AA, respiratory distress, or a critical form characterized by an acute respiratory distress syndrome or multivisceral failure. (7)

After infection, the incubation period is generally 5 to 7 days, and may, however, last between 1 and 14 days. (8)

This 2019 coronavirus infectious disease (COVID-19) spread rapidly around the world and on March 11th 2020, it was declared as a pandemic by the WHO. A global threat to our health systems and economic stability, its repercussions forced governments to take unprecedented health measures (9).

Faced with this urgent challenge, a plethora of research work was rapidly published (more than 332,000 publications referenced on PubMed) but at the cost of many biases. (10, 11) Despite great heterogeneities between studies (hospital capacities, health care systems, populations, epidemic phases, restrictive measures being different in each country), numerous markers discriminating the population most predisposed to develop severe and fatal forms have been identified. The WHO recognizes age over 65 and male gender, obesity, smoking, diabetes, cardiovascular diseases including hypertension, ischemic heart disease, stroke, COPD, and cancers, particularly hematological cancers, as risk factors for severe disease. (7) The French Haut Conseil de Santé Publique added to this list: chronic renal failure, chronic respiratory pathologies including, more broadly, severe asthma, pulmonary fibrosis, sleep apnea syndrome and cystic fibrosis; but also, congenital or acquired immunodepression, cirrhosis with a Child's score of at least B, sickle cell anemia, African ethnicity, the most disadvantaged socio-economic status, and neuromuscular pathologies. (12)

In order to optimize the management and allocation of medical resources in our overcrowded hospitals, the search for predictive factors of severity remained crucial. In a retrospective multicenter study by Carmichael et al (13), only initial hypoxia was predictive for intubation within 48 hours. However, many patients with hypoxia will show few signs, often referred to as "silent hypoxemia" or "happy hypoxia". (14,15)

A review of meta-analyses of the literature on predictive factors of poor outcomes (PubMed: "COVID" + "predict") shows many trends:

- In addition to the emergence of neutrophil/lymphocyte ratio, increased CRP and PCT, biological markers significantly associated with an increased risk of severity and mortality

included increased troponin, ASAT, CPK, LDH, Ddimer, PT, interleukin 6 and 10, blood glucose; but also, a decrease in lymphocytes, platelets, and albumin mainly.

- The associated comorbidities were male gender, age, cardio and cerebrovascular diseases, COPD, chronic renal disease, arterial hypertension, obesity, and diabetes mainly.

- Symptoms of chest pain and dyspnea.

Review of 54 meta-analyses of predictive factor studies. (September 2022)

| Parameters | ICU Admission | Mortality | Poor Outcomes |
|---------------------------|---------------|-----------|---------------|
| <i>Comorbidities</i> | | | |
| Ageing | +++ | +++ | + |
| Male gender | ++ | | + |
| Obesity | ++ | | ++ |
| Stroke | +++ | + | ++ |
| High Blood pressure | +++++ - | + | +++++ |
| Diabetes | +++++ - | - | +++ |
| Chronic renal failure | +++ - | + - | ++ |
| COPD | ++++ - | | +++ |
| Smoking | ++ - | ++ | |
| Cardiovascular diseases | +++++ - | + | +++ |
| Asthma | | - | |
| Liver disease | | - | |
| Cancer | +++ | - | ++ |
| Chronic lung disease | + - | + | + |
| Immunosuppressants | | - | |
| <i>Initial signs</i> | | | |
| Chest pain | + | + | |
| Dyspnea | +++ | +++ | + |
| Fever | + | | +++ |
| Diarrhea | + | | |
| Asthenia | + | ++ | |
| Anorexia | + | | |
| Myalgias | | + | |
| Sputum | | ++ | |
| Nausea | | + | |
| Hemoptysis | | + | |
| <i>Vital Signs</i> | | | |
| SpO2 AA <89% | | ++ | |
| Respiratory Rate ↑ | + | | |
| Systolic blood pressure ↑ | + | | |
| <i>Biology</i> | | | |
| Ratio N/L ↑ | +++++ | + | ++ |
| White Blood cells ↑ | +++++ - | +++++ | +++ |
| Lymphocytes ↓ | +++++ | +++ | + |
| Neutrophils ↑ | +++ | +++ | |
| Hemoglobin | + (↓) | + (↑) | |

| | | | |
|----------------------|--------|-------|-------|
| Platelets ↓ | ++++ | - - | + - |
| Platelets ↑ | | + | |
| Eosinophils ↓ | + | | |
| CRP ↑ | +++++ | +++ | ++ |
| PCT ↑ | +++++ | ++++ | ++ |
| Sédimentation rate ↑ | ++++ | + | + |
| IL 6 ↑ | +++ - | ++ | + |
| IL 10 ↑ | ++ | | |
| LDH ↑ | +++++ | ++ - | ++ |
| Albumin | ++ (↓) | + (↑) | + (↓) |
| Blood Glucose ↑ | ++ | + | |
| HbA1c ↑ | | - | |
| Ddimers ↑ | +++++ | ++++ | ++++ |
| CPK ↑ | ++++ - | + | +++ - |
| Creatinine ↑ | ++++ | +++ | + |
| Urea ↑ | + | + | + |
| Ferritin ↑ | ++++ | + | |
| Fibrinogen ↑ | ++ | | |
| Natremia ↓ | + | | |
| Bilirubin ↑ | ++ | | |
| ASAT ↑ | +++++ | ++ | +++ |
| ALAT ↑ | +++++ | ++ - | |
| Myoglobin ↑ | + - | + | + |
| Troponin ↑ | ++ - | +++++ | ++++ |
| BNP, NTproBNP ↑ | + | +++ | ++ |
| INR ↑ | | | + |
| PT ↓ | + | | + |
| Vitamin D ↓ | | + | |

Legend: + = significantly associated in the results of the meta-analysis;
 - = non-association highlighted in the results of the meta-analysis.
 (Bibliography: appendix 1)

Ageing is undoubtedly a predominant factor of vulnerability to severe forms of COVID19 and death. The population of the Principality of Monaco, with its unique socio-economic profile, has the highest life expectancy in the world (86.5 years in 2019 according to the Monegasque demographic observatory) (16). Does this specificity modify risk factors? Can we early identify among hospitalized patients those most likely to develop a critical form?

The aim of this study was to describe the clinical and biological characteristics of patients hospitalized for a moderate form of pneumo-COVID in the Princess Grace Hospital in order to identify the factors associated with aggravation of the clinical condition on the basis of two identifiable events: the transfer to the intensive care unit, or the occurrence of death.

Material and methods

This single-center retrospective observational study was conducted from September 1st, 2020 to April 14th, 2021 in the pneumo-COVID unit of the Princess Grace Hospital (CHPG) in Monaco.

- Population

All adult patients (>18 years-old) with a positive SARS-CoV-2 RT-PCR and a set of clinico-radiological arguments evocative of COVID-19, hospitalized during the second and third Monegasque epidemic waves, were consecutively screened using a computer database from the medical information department (DIM, FB). The recruitment was carried out from September 1st 2020, because it was the date on the reopening of the dedicated *pneumo-covid unit*¹, with a highly standardized medical care at the CHPG.

Standardization of medical care was allowed, among others, by an every morning multidisciplinary meeting for decisions makings where every patient was discussed by the *pneumo-covid unit* medical staff, infectiologists, resuscitators, palliative care physicians, emergency physicians, and paramedical staff including caregivers and nurses. Diagnostic, therapeutic, discharge or social/rehabilitation decisions were made, as well as limiting and stopping active therapies (LATA) when justified.

The exclusion criteria were as follows:

- Direct entry into the ICU without prior hospitalization in a medical unit (*pneumo-covid unit* or others).
- Positive RT-PCR, but asymptomatic patient hospitalized for any other reason.
- Several stays: only the first one is considered.

- Data collection

The data were collected and recorded in an Excel table by a single investigator (VP) from computerized hospital records (emergency observation, medical observation of the unit, biology, imaging) and paper records (nursing care record). A second investigator (GC) checked the adequacy of the reports.

From the computerized file we collected:

¹ This unit was firstly opened on March 17th, 2020 with the occurrence of the first wave in Monaco, and closed on May 30th, 2020.

- The initial chest CT-scan injury based on the radiologist's report or, failing that, the interpretation of the *pneumo-covid unit* doctors. When the damage was expressed as a range of percentages, the highest was considered.

- The biology is that carried out in the emergency room of the CHPG or the referring establishment, the missing data are completed with the first standardized re-evaluation biology during the first 48 hours of hospitalization.

The biological parameters collected are the followings: BCC (hemoglobin, hematocrit, leucocytes and distribution of leukocyte lineages, platelets), fibrinogen, PT, APTT ratio, Ddimer, natremia, kalemia, chloremia, blood glucose, calcemia, phosphoremia, magnesia, proteinemia, ultra-sensitive troponin, NTproBNP, ASAT, ALAT, γ GT, lipase, LDH, CRP, PCT, uremia, creatininemia. Glomerular filtration rate (GFR) is calculated using the CKD-EPI formula (17).

- Date of the onset of symptoms, of positive RT-PCR, of the initial symptomatology, previous therapies from the history of the emergency doctors and the *pneumo-covid unit* doctors.

- The presence of comorbidities among age >67 years, known chronic kidney disease, atrial fibrillation, hypertension, ischemic heart disease, peripheral artery disease, diabetes, COPD, asthma, chronic respiratory failure, smoking, cancer, cognitive disorders, stroke, sleep apnea syndrome.

- Vitals (respiratory rate, SpO₂, heart rate, systolic and diastolic blood pressure, temperature) in the emergency room recorded by the reception nurse.

From the paper records we collected:

- Weight and height as transcribed by the ward nurse. Body mass index was calculated as weight (kg) divided by height squared (m²) and obesity was defined as BMI>30 kg/m².

- Autonomy according to the nursing file grid.

- Vitals (respiratory rate, SpO₂, heart rate, systolic and diastolic blood pressure, temperature) on arrival in the department as well as the oxygen-requirement.

- Between group comparisons.

Aggravation of the clinical condition was defined as two identifiable events: death; or transfer to the ICU because of a critically worsening condition.

For the analysis of factors associated with death, the study population was divided into two groups, and patients who died were compared with those who survived.

For the analysis of factors associated with the transfer to the ICU, LATA patients were firstly excluded from the analysis (because they would not be transferred to the ICU, by definition), and critically worsening patients, i.e. those who were transferred to the ICU, were compared with the non-critically worsening patients.

- Statistical analysis (FB, GC)

After the collection of parameters, all data were anonymized. The clinico-pathological demographic characteristics are presented for the entire population and by subgroups. Categorical variables are expressed as numbers (%). Normally distributed continuous parameters are described as mean \pm standard deviation (SD) (ranges).

Univariate comparative statistical analysis is performed using the Chi² test for categorical variables and the Student t test for continuous variables. To adjust for risk factors associated with disease progression in hospital, an initial multivariate logistic regression analysis based on the results of the univariate analyses was performed (not shown). A multivariate logistic regression model was also constructed to identify the factors associated with death vs survival on the one hand, and critically worsening vs non-critically worsening on the other hand. The selection of variables included in the model met the following criteria: risk factors recognized as being relevant in the medical literature, variables that were clinically relevant and significantly associated to the endpoints in univariate analysis, and a lack of high collinearity. A p-value < 0.05 was considered statistically significant.

Statistical analyses were performed using JMP 14 software and, for multivariate analyses, SAS 9.1. (SAS Institute, Cary, North Carolina, USA).

- Ethical considerations

The authors declared no conflicts of interest in this study.

This study was conducted in accordance with the Declaration of Helsinki.

In accordance with the French law n°2004-806 of 9 August 2004, applicable at the time of data collection and writing of the study, the research did not require approval by an ethics committee.

Results

During the study period, 389 patients were hospitalized in the CHPG *pneumo-covid unit* (Figure 1). Thirty-two of them were excluded from our study: 22 patients because they had entered directly into the intensive care unit, prior to being transferred to the *pneumo-covid unit*, 8 patients because they were asymptomatic, hospitalized for other reasons (sleep apnea syndrome exploration, lung cancer, femur fracture, intestinal occlusion) and hosted in the unit only for protective isolation, and 2 patients who stayed twice: their second stay was not considered.

The study population therefore comprises 357 patients, including 36 deaths during the study period. For 25 among those 357 patients, collegial discussions led to the decision of limiting and stopping active therapies (LATA): these patients were *de facto* not eligible for resuscitation and were thus excluded from the analysis comparing critically worsening (transfer to the ICU) vs non-critically worsening patients.

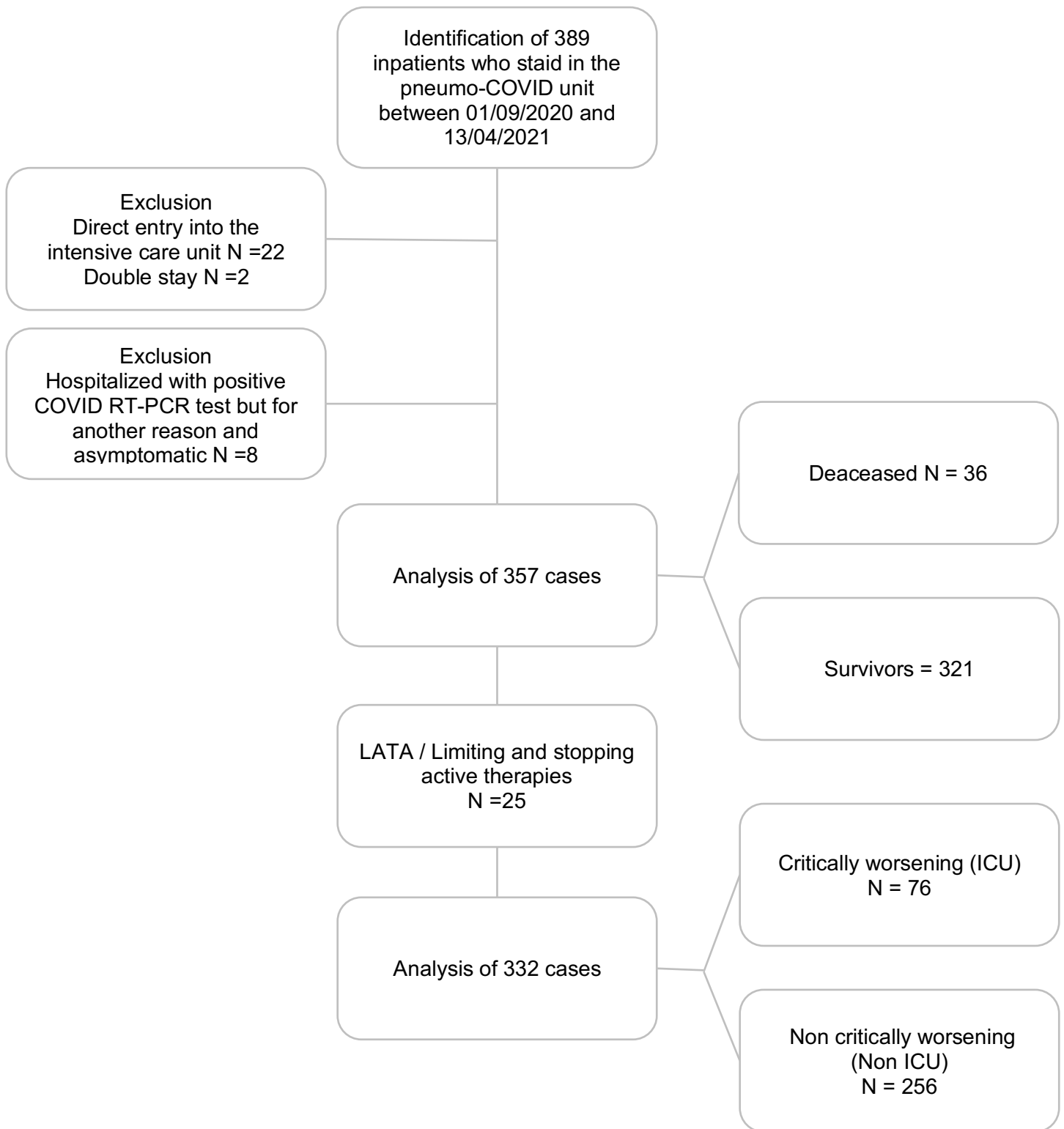


Figure 1 - Flowchart summarizing the inclusion process of the study population and subgroups analyses.

Description of the initial features of the study population.

Characteristics of the study population are shown in Table 1.

The 357 patients included ranged in age from 30 to 97 years, with a mean age of 68.4 years. The majority were men (56.8%) and most had about two comorbidities (actually 2.3 on average). In ascending order: age>67 years old (54.9%, n=196), hypertension (40.3%, n=144), obesity (22.1%, n=79), diabetes (17.6%, n=63), active or cured cancer pathology (17.4%, n=62) including 9 hemopathies, ischemic heart disease (16.0%, n=57), atrial fibrillation (14.6%, n=52), COPD (10.6%, n=38), chronic kidney disease (9, 8%, n=35) of whom 4 were on long-term dialysis, cognitive disorders (8.4%, n=30), smoking (7.6%, n=27), asthma (6.7%, n=24), sleep apnea syndrome (6.2%, n=22), cerebrovascular disease (6.2%, n=22), PAD (3.4%, n=12), and chronic respiratory insufficiency (3.1%, n=11) of whom 6 were on home oxygen therapy.

The dominant symptomatology on admission was altered general condition (84.9%), cough (66.4%), fever (61.1%) and dyspnea (60.2%). Digestive signs (29.7%), headache (26.3%), anosmia/ageusia (19.6%) and myalgia (18.2%) were present in less than one third of the hospitalized patients. Patients presented within one week of the onset of their symptoms. A quarter had received pre-hospital antibiotic therapy (23.0%).

Except for 6 patients, lung CT scan was performed in 98.3% of the patients, half of them with injection of contrast agent. Estimated involvement ranged from zero to 75% with an average of 27.7%.

From the point of view of autonomy, only seven patients were bedridden (1.97%), thirty-one (8.71%) were dependent for activities of daily living, 60 patients (16.85%) had home help and the majority were autonomous (56%; n=258).

Patients with an unfavorable outcome represented 28% of the population studied, i.e. a total of 100 individuals, of which 76 transfers to intensive care and 36 deaths (including 12 deaths in intensive care). Overall mortality was 10%. The average time to transfer in intensive care unit was 3.4 days, with a minimum of zero day and a maximum of 14 days after admission to the COVID unit.

Table 1 - Characteristics of the study population (n=357)

| | Mean \pm SD (min - max) or n (%) | missing data |
|---|---|--------------|
| Anthropomorphic data | | |
| Age, years | 68,35 \pm 15,73 (30,5 - 97,9) | |
| Male gender | 203 (56,8) | |
| Weight, kg | 76,75 \pm 17,25 (35 - 140) | 5 |
| Height, m | 1,69 \pm 0,09 (1,41 - 1,9) | 3 |
| BMI, kg/m ² | 26,61 \pm 4,94 (12,7 - 45,7) | 5 |
| Poor prognosis events/decision | | |
| Death | 36 (10) | |
| Admitted to ICU | 76 (21) | |
| LATA | 25 (7) | |
| Chronology | | |
| Duration of stay (days) | 12,7 \pm 11,8 (0 - 95) | |
| Delay 1 st symptoms-admission (days) | 6,98 \pm 4,72 (0 - 31) | |
| Delay transfer to ICU (days) | 3,41 \pm 2,9 (0 - 14) | |
| Delay 1 st symptoms-transfer to ICU (days) | 9,78 \pm 4,36 (0 - 30) | |
| Comorbidities | | |
| Comorbidities (number) | 2,3 \pm 1,8 (0 - 8) 0 = 65 ; 1 = 84 ; 2 = 60 ; 3 = 53 ; 4 = 43 ; 5 = 32 ; 6 = 13 ; 7 = 5 ; 8 = 2 | |
| Age > 67 years | 196 (54,9) | |
| Hypertension | 144 (40,3) | |
| Obesity | 79 (22,1) | |
| Cancer | 63 (17,6) | |
| Diabetes | 62 (17,4) | |
| Ischemic heart disease | 57 (16,0) | |
| Atrial fibrillation | 52 (14,6) | |
| COPD | 38 (10,6) | |
| Chronic kidney disease | 35 (9,8) | |
| Active smoking | 30 (8,4) | |
| Asthma | 27 (7,6) | |
| SAS | 24 (6,7) | |
| Cognitives disorders | 22 (6,2) | |
| Cerebrovascular disease | 22 (6,2) | |
| PAD | 12 (3,4) | |
| Chronic Respiratory Failure | 11 (3,1) | |

| <i>Imaging</i> | | |
|-----------------------------------|--|--------------------------------------|
| Thoracic unenhanced CT scan | | 176 (49,3) |
| Pulmonary angio-CT scan | | 175 (49,0) |
| Lung involvement (parenchymal %) | | 27,7 ±18 (0-75) |
| Diagnosed pulmonary embolism | | 16 (4,5) |
| <i>Biology</i> | | |
| Hemoglobin, g/dL | | 13,2 ± 1,71 (4,7 - 17,3) |
| Hematocrit, % | | 39,1 ± 4,6 (14,9 - 49,9) |
| Leukocytes, G/L | | 6,72 ± 6,2 (0,93 - 105,86) |
| Neutrophils, G/L | | 4,97 ± 3,4 (0,3 - 33,3) 1 |
| Lymphocytes, G/L | | 1,06 ± 1,17 (0,17 - 18,6) 1 |
| N/L Ratio | | 6,66 ± 6,15 (0,14 - 37,8) 1 |
| Eosinophils, G/L | | 0,03 ± 0,07 (0 - 0,77) 1 |
| Basophils, G/L | | 0,015 ± 0,01 (0 - 0,11) 1 |
| Platelets, G/L | | 205,9 ± 88,7 (28 - 722) |
| PT, % | | 75,6 ± 18,8 (10 - 100) 2 |
| APTT Ratio | | 1,3 ± 0,6 (0,73 - 8,5) 3 |
| Fibrinogen, g/L | | 4,98 ± 1,4 (1,81 - 8,7) 14 |
| D-dimer, ng/mL | | 1288 ± 1589 (215 - 7650) 21 |
| Natremia, mmol/L | | 135,6 ± 4,1 (114 - 151) |
| Kalemia, mmol/L | | 3,98 ± 0,47 (2,7 - 5,7) |
| Chloremia, mmol/L | | 99 ± 4,1 (82 - 116) |
| Protidemia, g/L | | 70,9 ± 5,6 (51 - 90) 1 |
| Uremia, mmol/L | | 7,24 ± 4,24 (1,21 - 37,8) 1 |
| Creatininemia, µmol/L | | 93,9 ± 49,3 (22,5 - 464) |
| Blood glucose, g/L | | 1,33 ± 0,48 (0,75 - 3,6) 46 |
| Calcemia, mmol/L | | 2,2 ± 0,16 (1,13 - 2,76) 41 |
| Phosphoremia, mmol/L | | 0,9 ± 0,2 (0,3 - 2,1) 88 |
| Magnesia, mmol/L | | 0,84 ± 0,1 (0,47 - 1,3) 79 |
| CKDEPI calculated, mL/min | | 69,7 ± 22,2 (6,8 - 107,9) |
| ASAT, UI/L | | 47 ± 29,1 (10 - 254) 3 |
| ALAT, UI/L | | 35,4 ± 30,3 (5 - 261) 4 |
| GGT, UI/L | | 73,4 ± 86,1 (9 - 815) 6 |
| Lipase, UI/L | | 50,2 ± 46,9 (6,1 - 490) 166 |
| Troponin, ng/L | | 0,02 ± 0,03 (0,003 - 0,27) 78 |
| NT-pro-BNP, pg/mL | | 1639 ± 6562 (5 - 70 000) 23 |
| CRP, mg/L | | 69,1 ± 58,6 (0,3 - 384) |
| PCT, ng/mL | | 0,24 ± 0,59 (0,02 - 6,57) 27 |
| LDH, UI/L | | 325,2 ± 112,5 (168 - 839) 292 |
| <i>Pre hospital therapies</i> | | |
| Prehospital Antibiotic therapy | | 82 (23,0) |
| Prehospital Corticosteroid /NSAID | 56 (15,7) NSAID = 4 ; CTC = 52 ; Both = 1 | |
| <i>Degree of independence</i> | | |

| | |
|-------------------|--------------------|
| Autonomous | 258 (72,47) |
| Assisted | 60 (16,85) |
| Dependent | 31 (8,71) |
| Grabber | 7 (1,97) |

Vital constants at emergency

| | | |
|---------------------------------------|---|-----------|
| Respiratory Rate, c/min | 22,8 ± 6,2 (11 - 50) | 97 |
| SpO₂, % | 93 ± 4,9 (65 - 100) | 15 |
| Oxygenotherapy, L/min | 0,1 ± 0,6 (0 - 6) | 15 |
| | 0 = 339 ; 1 = 3 ; 2 = 4 ; 3 = 1 ; 4 = 2 ; 6 = 2 | |
| | including 5 patients LTO | |
| Systolic Blood Pressure, mmHg | 141 ± 25,9 (57 - 254) | 21 |
| Diastolic Blood Pressure, mmHg | 78 ± 14,3 (45 - 148) | 21 |
| Heart Rate, b/min | 87,9 ± 17,4 (49 - 165) | 15 |
| Temperature, °C | 37,6 ± 0,86 (35 - 40) | 25 |

Vital constants on arrival in the pneumo-covid unit

| | | |
|---------------------------------------|--------------------------------|-----------|
| Respiratory Rate, c/min | 21,1 ± 4,5 (12 - 35) | 25 |
| SpO₂, % | 95,5 ± 2,1 (87 - 100) | 0 |
| Oxygenotherapy, L/min | 1,8 ± 2,25 (0 - 15) | 0 |
| Systolic Blood Pressure, mmHg | 130,6 ± 21,3 (80 - 195) | 1 |
| Diastolic Blood Pressure, mmHg | 74,5 ± 11,6 (40 - 125) | 1 |
| Heart Rate, b/min | 81,7 ± 13,9 (32 - 138) | 1 |
| Temperature, °C | 37,2 ± 0,8 (36 - 40,5) | 4 |

Initial signs

| | |
|-------------------------|-------------------|
| Asthenia/malaise | 303 (84,9) |
| Cough | 237 (66,4) |
| Headache | 94 (26,3) |
| Dyspnea | 215 (60,2) |
| Myalgia | 65 (18,2) |
| Digestive signs | 106 (29,7) |
| Fever | 218 (61,1) |
| Anosmia/Agueusia | 70 (19,6) |

Comparison between critically worsening (transferred to ICU) vs non-critically worsening patients (LATA excluded, n=332)

Univariate analysis of the comparison between both subgroups is shown in Table 2.

The 76 patients progressing to ICU transfer were significantly older (71.0 vs 65.6 years; $p=0.0063$), more likely to be male (72.4 - 53.5%; $p=0.0029$), and of higher weight (81.6 vs 76.2kg; $p=0.0171$) without creating a significant difference in BMI ($p=0.0544$). The total number of comorbidities was higher (2.75 vs 1.97) with a higher percentage of history of hypertension (50.67 vs 34.12%; $p=0.0102$) and peripheral arterial disease (6.58 vs 1.56%; $p=0.0318$) in the intensive care group.

CT lung parenchymal involvement was also statistically significantly higher (33.1 vs 25.9%; $p=0.0025$) with no significant difference in the proportion of pulmonary embolism detected ($p=0.4311$).

The comparison of biological results at entry showed in the group of patients transferred to intensive care: a stronger inflammatory syndrome with higher CRP and PCT markers, respectively 93,4 vs 61,2 mg/L ($p < 0,0001$) and 0,38 vs 0,19 ng/mL ($p=0,0205$). There was an increase in the neutrophil to lymphocyte ratio (7,66 vs 6,06 ; $p=0,0410$) resulting from a significant increase in neutrophils (5,45 vs 4,64 G/L ; $p=0,0455$). We also found eosinopenia (0.01 vs 0.03 G/L; $p=0.0406$) and a greater decrease in platelet count in this group (181.8 vs 213.3 G/L; $p=0.0061$). The renal function of patients transferred to the ICU was also significantly impaired with increased urea and creatinine (8,00 vs 6,67mmol/L ; $p=0,0120$ and 101,8 vs 88,5 $\mu\text{mol/L}$; $p=0,0274$). As a result, the filtration rate was mathematically decreased (63,6 vs 73,8; $p=0,0002$).

Blood glucose values was higher (1.46 vs 1.26 g/L; $p=0.0012$) despite no significant difference in the proportion of previous diabetes (21 vs 14,5%; $p=0,1790$). We observed a decrease in phosphorus levels (0.83 vs 0.93mmol/L; $p=0.0067$) isolated to the blood ionogram. ASAT only for the liver enzyme and LDH were significantly increased (54 vs 46 IU/L; $p=0.0303$ and 349 vs 270 IU/L; $p=0.0006$ respectively).

Among the other factors studied, we identify a lower ambient air saturation on admission (90.9% on average vs 94.0%; $p < 0.001$), as well as differences in respiratory parameters at entry to the ward, namely Respiratory Rate (22,2 vs 20,8 /min ; $p=0,0229$), pulse oxygen saturation (94,9 vs 95,8% ; $p=0,0004$) and oxygen demand (2,99 vs 1,25 L/min ; $p < 0,0001$).

Pre-hospital prescription of antibiotics or anti-inflammatory drugs did not affect patient outcomes ($p=0.2369$ and $p=0.4617$). There was no significant difference between the time of symptom onset and hospital admission in the two groups.

Anosmia-ageusia, which may be a feature of ENT disease, appeared to be protective ($p=0.0182$).

Mortality was more than 5 times higher in the ICU (2.73 vs 15.79% - $p=0.001$).

In a multivariate analysis which simply included the various statistically significant items from the univariate analysis (age, sex, weight, number of comorbidities, high blood pressure, OSA, CT scan, blood glucose, blood phosphorus, CRP, urea, creatinine, PCT, eosinophils, neutrophils, platelets, ASAT, SpO₂ at the time of entry into the emergency department, respiratory rate on arrival in the department, anosmia and dyspnea), The presence of arterial occlusive disease of the lower limbs ($p=0.0068$), CT scan of the upper lung parenchyma ($p=0.0393$), lower pulse oxygen saturation in the emergency department ($p=0.0155$), and lower phosphorus ($p=0.0398$), increased procalcitonin ($p=0.0158$) and eosinopenia ($p=0.0378$) were all independently associated with a move to the ICU.

Using a statistical model to limit confounding effects and bias (Table 4a), we found a "protective" effect of female gender with an OR of 0.285 (95%CI: 0.117 - 0.692; $p=0.0056$). Eosinopenia (below laboratory threshold: $< 40/\text{mm}^3$ for men and $< 20/\text{mm}^3$ for women) (OR = 3.166; 95%CI: 1.005 - 9.975; $p=0.0491$) and room air pulse saturation ($p=0.003$) with an OR of 2.842 (95%CI: 1.059 - 7.629 for values between 90 and 95% and an OR of 7.537 for values below 90% 95%CI: 2.361 - 24.065) remain significantly associated with ICU admission. Phosphorus appeared to be a factor close to significance ($p=0.0583$) with an OR of 0.691 for a variation of 0.2 mmol/L (95% CI: 0.471 - 1.013). The comorbidities tested (high blood pressure, diabetes, cancer, cardiovascular pathologies and chronic respiratory pathologies as a whole) were not at all discriminating, as were inflammation markers and age ($p=0.7619$).

Comparison between deceased patients and survivors.

The LATA patients reintegrated in this part of the study were 44% male, with a mean age of 88 years (± 6.44), and with an average of 4.5 comorbidities distributed as follows: High blood pressure (76%, $n=19$), diabetes (40%, $n=10$), cognitive disorders (52%, $n=13$), stroke (28%, $n=7$), atrial arrhythmia (36%, $n=9$), ischemic heart disease (44%, $n=11$), PAD (12%, $n=13$), chronic respiratory failure (12%, $n=3$) of which 2 on long-term oxygen, cancer (32%,

n=8), chronic renal failure (32%, n=8) and obesity (4%, n=1) for an average BMI of 24,8kgm/m². All of them underwent thoracic imaging, of which only five (20%) were injected with iodinated contrast, revealing lung parenchymal involvement in 29.4% (+/-25).

Univariate comparison between deceased patients and survivors is shown in Table 3.

Compared to survivors, patients who unfortunately died were older (83.1 vs 66.7 years; p <0.0001), with more comorbidities (3.5 vs 2.2; p=0.0394). Renal failure (p=0.0187), high blood pressure (p=0.0088), ischemic heart disease (p=0.0017), cognitive disorders (p=0.0002), stroke (p <0.0001) and cancer (p=0.0011) were significantly overrepresented. In contrast, obesity (p=0.0041), asthma (p=0.279) and sleep apnea syndrome (p=0.0214) were in lower proportion in the group of decedents. CT lung parenchymal involvement was more marked in the latter group (37.8 - 26.5%; p=0.0006).

In terms of biological markers, hemoglobin (12.3 vs 13.3g/dL; p=0.0006) and hematocrit (37.1 vs 39.3%; p=0.0079), PT (68.6 vs 76.4%; p=0.197), and glomerular filtration rate (48.6 vs 72mL/min; p<0.0001) in line with the preponderance of previous renal failure, were significantly lower in patients progressing to death.

In opposition we observe an increase in leukocytes (10.5 vs 6.3G/L; p<0.001), neutrophils (p=0.0143) and lymphocytes (p=0.0037) and also in the N/L ratio (8.9 vs 6.4; p=0.0186); The APTT ratio (1.64 vs 1.29; p=0.0004), Ddimer (2311 vs 1188ng/mL; p=0.0002), LDH (464.1 vs 308.4 IU/L; p=0.0003), blood glucose (1.5 vs 1.3 g/L; p=0.0113) show the same trend. Inflammatory biomarkers: CRP (98 vs 65.9 mg/L; p=0.0017) and PCT (0.6 vs 0.2 ng/mL; p=0.0004); cardiac biomarkers: Troponin (0.07 vs 0.016 ng/L; p=<0.0001) and NTproBNP (8771 vs 910 pg/mL; p=<0.0001), and renal biomarkers: Urea (11.38 vs 6.77 mmol/L; p<0.0001) and creatinine (127.1 vs 90.1 umol/L; p<0.0001) observed significantly higher values.

On admission, respiratory parameters (respiratory rate, pulse oxygen saturation and oxygen delivery rate) were more degraded in the emergency department and in the ward in the group of patients who died. For a significantly higher respiratory rate (26.1 vs 22.5 c/min in the emergency department; p=0.0088 and 24 vs 20.8 c/min in the COVID unit) and despite higher oxygen therapy (3.5L vs 1.6 L/min on arrival in the department; p<0.0001), pulsed oxygen saturation was significantly lower (89.4 vs 93.4% in the emergency department; p<0.0001 and 95.6 vs 94.5% on arrival in the COVID unit; p=0.0013).

Heart rate was higher in the emergency department (93.8 vs 87.2; p=0.0373) and on arrival at the unit (86.6 vs 81.1; p=0.0244), but still within the normal range.

Symptoms of cough ($p=0.0125$) and anosmia/ageusia ($p=0.0114$) were fewer common complaints in the decedents group.

Pre-hospital administration of corticosteroids was three times more frequent in the survivors than in the deceased (15.2% vs 5.56%; $p=0.0483$). Patients in the decedents group were admitted to hospital earlier than survivors (4.28 vs 7.29 days; $p=0.0003$).

After adjustment by multivariate analysis (Table 4b), age ($p=0.0033$) was independently associated with mortality with an OR of 3.45 [95%CI: 1,510 - 7,884] for a 10-year increase; thrombocytopenia ($p=0.0195$), kalemia ($p=0,0181$) with an OR of 4.14 (95% CI: 1.275 - 13.441) for an increase of 1 mmol/L; and higher scanographic damage ($p=0.043$) with an OR of 3.955 for a threshold of 40% (95% CI: 1.044 - 14.982). The Odds Ratio for platelets was 0.574 (95% CI: 0.360 - 0.915) for a 50,000 element/m³ increase.

By including phosphorus in the logistic regression model (Table 4c), increasing the number of missing data (33% of patients with at least one missing data item), CT involvement obtained an OR of 4.46 (95% CI: 0.832 - 23.895; $p=0.0809$) and lost significance. Age, kalemia and platelets remained associated with mortality, and in addition CRP with an OR of 3.51 (95% CI: 1.311 - 9.396; $p=0.0125$) for an increase of 50mg/L and hemoglobin, for an increase of 1g/dL, the OR is 0.459 (95% CI: 0.023 - 0.915; $p=0.0270$). The presence of hypertension was inversely associated with an OR of 0.153 (95% CI: 0.024 - 0.966; $p=0.0458$).

Table 2 - Comparison of critically worsening (transferred to ICU) and non-critically worsening patients.

| | Critically worsening N = 76 | | Non-critically worsening N = 256 | | <i>p</i> |
|---|--------------------------------|---------|--|---------|-----------------|
| <i>Anthropomorphic data</i> | | | | | |
| Age, mean (SD) | 71 | (11) | 65,6 | (16,1) | 0,0063 |
| Male gender, n (%) | 55 | (72,4) | 137 | (53,5) | 0,0029 |
| Weight, mean (SD) | 81,58 | (16,48) | 76,17 | (17,49) | 0,0171 |
| Height, mean (SD) | 1,71 | (0,09) | 1,69 | (0,09) | 0,0656 |
| BMI, mean (SD) | 27,7 | (4,88) | 26,4 | (4,98) | 0,0544 |
| <i>Evolution</i> | | | | | |
| Length of stay, mean (SD) | 24,86 | (15,97) | 8,98 | (7,23) | < 0,0001 |
| Death, n (%) | 12 | (15,79) | 7 | (2,73) | 0,0001 |
| Delay 1 st symptoms - admission, mean (SD) | 6,4 | (4,6) | 7,5 | (4,7) | 0,0847 |
| <i>Comorbidities</i> | | | | | |
| Comorbidities, mean (SD) | 2,75 | (1,77) | 1,97 | (1,76) | 0,0008 |
| Renal failure, n (%) | 7 | (9,21) | 20 | (7,81) | 0,6992 |
| Age > 67 years, n (%) | 49 | (64,47) | 122 | (47,66) | 0,0095 |
| Atrial Arrhythmia, n (%) | 30 | (39,47) | 30 | (11,72) | 0,2323 |
| High Blood Pressure, n (%) | 38 | (50,00) | 87 | (33,98) | 0,0102 |
| Ischemic Heart Disease, n (%) | 15 | (19,74) | 31 | (12,11) | 0,1025 |
| PAD, n (%) | 5 | (6,58) | 4 | (1,56) | 0,0318 |
| Obesity, n (%) | 23 | (30,26) | 55 | (21,48) | 0,1203 |
| Chronic Respiratory failure, n (%) | 3 | (3,95) | 5 | (1,95) | 0,3469 |
| COPD, n (%) | 12 | (15,79) | 23 | (8,98) | 0,1037 |
| SAS, n (%) | 6 | (7,89) | 16 | (6,25) | 0,6195 |
| Asthma, n (%) | 5 | (6,58) | 19 | (7,42) | 0,8013 |
| Smoking, n (%) | 7 | (9,21) | 18 | (7,03) | 0,5362 |
| Diabetes, n (%) | 16 | (21,05) | 37 | (14,45) | 0,179 |
| Cancer, n (%) | 15 | (19,74) | 39 | (15,23) | 0,3591 |
| Cognitive disorders, n (%) | 2 | (2,63) | 15 | (5,86) | 0,2293 |
| Stroke n (%) | 4 | (5,26) | 11 | (4,30) | 0,7263 |
| <i>Imaging</i> | | | | | |
| Thoracic CT scan, n (%) | 33 | (43,42) | 123 | (48,05) | |
| Thoracic angioscan, n (%) | 42 | (52,26) | 128 | (50,00) | |
| Lung parenchymal involvement, mean (SD) | 33,1 | (19,1) | 25,9 | (17,4) | 0,0025 |
| Pulmonary embolism detected, n (%) | 5 | (6,58) | 10 | (3,91) | 0,4311 |
| <i>Biology</i> | | | | | |
| Hemoglobin, mean (SD) | 13,45 | (1,57) | 13,29 | (1,65) | 0,4554 |
| Hematocrit, mean (SD) | 39,7 | (4,3) | 39,1 | (4,5) | 0,3209 |
| Leukocytes, mean (SD) | 6,74 | (3,28) | 6,23 | (2,96) | 0,1995 |
| Neutrophils, mean (SD) | 5,45 | (4,14) | 4,64 | (2,68) | 0,0455 |

| | | | |
|---|------------------------|-----------------------|-------------------|
| Lymphocytes, mean (SD) | 1,19 (2,12) | 1,01 (0,58) | 0,2333 |
| N/L Ratio, mean (SD) | 7,66 (7,62) | 6,06 (5,36) | 0,041 |
| Eosinophils, mean (SD) | 0,01 (0,03) | 0,03 (0,07) | 0,0406 |
| Basophils, mean (SD) | 0,01 (0,01) | 0,01 (0,01) | 0,5854 |
| Platelets, mean (SD) | 181,8 (76,6) | 213,3 (90,3) | 0,0061 |
| PT, mean (SD) | 75,1 (16,9) | 76,2 (18,7) | 0,6755 |
| APTT ratio, mean (SD) | 1,35 (0,31) | 1,29 (0,46) | 0,2818 |
| Fibrinogen, mean (SD) | 5,28 (1,52) | 4,94 (1,36) | 0,0677 |
| D-dimer, mean (SD) | 1203 (1192) | 1212 (1597) | 0,9635 |
| Natremia, mean (SD) | 134,9 (5,0) | 135,6 (3,6) | 0,1381 |
| Kalemia, mean (SD) | 4,0 (0,5) | 4,0 (0,5) | 0,4385 |
| Chloremia, mean (SD) | 98,4 (4,2) | 99,1 (4,0) | 0,2197 |
| Protidemia, mean (SD) | 71,2 (5,4) | 70,9 (5,5) | 0,6617 |
| Uremia, mean (SD) | 8,00 (3,57) | 6,67 (4,18) | 0,012 |
| Creatininemia, mean (SD) | 101,1 (44,8) | 88,5 (43,2) | 0,0274 |
| Blood glucose, mean (SD) | 1,46 (0,38) | 1,26 (0,46) | 0,0012 |
| Calcemia, mean (SD) | 2,19 (0,14) | 2,20 (0,15) | 0,5752 |
| Phosphoremia, mean (SD) | 0,83 (0,22) | 0,92 (0,21) | 0,0067 |
| Magnesia, mean (SD) | 0,84 (0,12) | 0,85 (0,10) | 0,7001 |
| CKDEPI calculated, mean (SD) | 63,6 (19,4) | 73,8 (21,5) | 0,0002 |
| ASAT, mean (SD) | 54,07 (30,92) | 45,75 (28,77) | 0,0303 |
| ALAT, mean (SD) | 35,70 (26,9) | 36,57 (31,8) | 0,8275 |
| GGT, mean (SD) | 74,39 (69,44) | 74,05 (92,66) | 0,9765 |
| Lipase, mean (SD) | 53,01 (66,8) | 50,44 (37,0) | 0,7436 |
| Troponin, mean (SD) | 0,022 (0,028) | 0,017 (0,026) | 0,1466 |
| NT-pro-BNP, mean (SD) | 1524,4 (4167,8) | 959,5 (3751,2) | 0,2712 |
| CRP, mean (SD) | 93,96 (67,01) | 61,62 (54,79) | <0,0001 |
| PCT, mean (SD) | 0,38 (0,81) | 0,19 (0,52) | 0,0205 |
| LDH, mean (SD) | 349,1 (93,2) | 270,1 (72,9) | 0,0006 |
| <i>Pre hospital therapies</i> | | | |
| Prehospital Antibiotic therapy, n (%) | 22 (28,95) | 57 (22,27) | 0,2369 |
| Prehospital Corticosteroid /NSAID, n (%) | 15 (19,74) | 41 (16,02) | 0,4617 |
| <i>Degree of independence</i> | | | |
| Autonomous, n (%) | 57 (75,00) | 201 (78,52) | 0,0421 |
| Assisted, n (%) | 17 (22,37) | 35 (13,67) | |
| Dependent, n (%) | 1 (1,32) | 18 (7,03) | |
| Bedriden, n (%) | 0 (0) | 2 (0,78) | |
| <i>Vital constants at emergency</i> | | | |
| Respiratory Rate, mean (SD) | 24,0 (6,4) | 22,3 (6,1) | 0,0699 |
| SpO2, mean (SD) | 90,90 (4,33) | 93,96 (4,54) | <0,0001 |
| Oxygenotherapy, mean (SD) | 0,20 (0,79) | 0,06 (0,47) | 0,0673 |
| Systolic Blood Pressure, mean (SD) | 140,8 (26,0) | 140,6 (24,9) | 0,955 |
| Diastolic Blood Pressure, mean (SD) | 77,6 (15,1) | 78,6 (13,8) | 0,5962 |

| | | | | | |
|--|--------------|----------------|--------------|----------------|-------------------|
| Heart Rate, mean (SD) | 87,0 | (16,8) | 88,2 | (17,7) | 0,601 |
| Temperature, mean (SD) | 37,7 | (1,0) | 37,5 | (0,9) | 0,2231 |
| <i>Vital Constants on arrival in the pneumo-covid unit</i> | | | | | |
| Respiratory Rate, mean (SD) | 22,19 | (5,08) | 20,8 | (4,22) | 0,0229 |
| SpO2, mean (SD) | 94,9 | (1,8) | 95,8 | (2,1) | 0,0004 |
| Oxygenotherapy, mean (SD) | 2,99 | (2,44) | 1,25 | (1,50) | <0,0001 |
| Systolic Blood Pressure, mean (SD) | 133,6 | (22,2) | 129,3 | (21,1) | 0,1286 |
| Diastolic Blood Pressure, mean (SD) | 75,5 | (10,7) | 74,4 | (11,8) | 0,4747 |
| Heart Rate, mean (SD) | 81,1 | (13,4) | 81,5 | (14,0) | 0,6902 |
| Temperature, mean (SD) | 37,4 | (0,8) | 37,2 | (0,8) | 0,0289 |
| <i>Initial signs</i> | | | | | |
| Asthenia/malaise, n (%) | 67 | (88,16) | 217 | (84,77) | 0,4516 |
| Cough, n (%) | 52 | (68,42) | 175 | (68,36) | 0,9919 |
| Headache, n (%) | 19 | (25,00) | 73 | (28,52) | 0,5446 |
| Dyspnea, n (%) | 59 | (77,63) | 142 | (55,47) | 0,0004 |
| Myalgia, n (%) | 18 | (23,68) | 47 | (18,36) | 0,3124 |
| Digestive Signs, n (%) | 25 | (32,89) | 76 | (29,69) | 0,5954 |
| Fever, n (%) | 52 | (68,42) | 154 | (60,16) | 0,1883 |
| Anosmia/Agueusia, n (%) | 9 | (11,84) | 61 | (23,83) | 0,0182 |

Table 3 - Comparison of deceased patients and survivors

| | Deceased (36 - 10,1%) | | Survivors (321 - 89,9%) | | <i>p</i> |
|---|-----------------------|--------|-------------------------|---------|-------------------|
| <i>Anthropomorphic data</i> | | | | | |
| Age, mean (SD) | 83,1 | (1,6) | 66,7 | (15,4) | <0,0001 |
| Male gender, n (%) | 20 | (55,6) | 183 | (57,0) | 0,8675 |
| Weight, mean (SD) | 68,7 | (10,4) | 77,6 | (17,6) | 0,0048 |
| Height, mean (SD) | 1,66 | (0,09) | 1,69 | (0,09) | 0,0178 |
| BMI, mean (SD) | 25,0 | (3,0) | 26,8 | (5,1) | 0,0567 |
| <i>Evolution</i> | | | | | |
| Length of stay, mean (SD) | 16,5 | (13,4) | 12,3 | (11,5) | 0,0394 |
| Delay 1st symptoms - admission, mean (SD) | 4,28 | (4,14) | 7,29 | (4,7) | 0,0003 |
| Admitted to ICU, n (%) | 13 | (36,1) | 64 | (19,93) | 0,0343 |
| Delay admission - transfer to ICU, mean (SD) | 3,77 | (3,0) | 3,34 | (2,9) | 0,6834 |
| Delay 1st symptoms - transfer to ICU, mean (SD) | 8,6 | (4,9) | 10 | (4,2) | 0,2891 |
| <i>Comorbidities</i> | | | | | |
| Comorbidities, mean (SD) | 3,5 | (1,52) | 2,2 | (1,84) | <0,0001 |
| Renal failure, n (%) | 8 | (22,2) | 27 | (8,4) | 0,0187 |
| Age > 67 years, n (%) | 33 | (91,7) | 163 | (50,8) | <0,0001 |
| Atrial Arrhythmia, n (%) | 7 | (19,4) | 45 | (14,0) | 0,3988 |
| High Blood Pressure, n (%) | 22 | (61,1) | 122 | (38,0) | 0,0088 |
| Ischemic Heart Disease, n (%) | 13 | (36,1) | 44 | (13,7) | 0,0017 |
| PAD, n (%) | 3 | (8,3) | 9 | (2,8) | 0,1305 |
| Obesity, n (%) | 2 | (5,6) | 77 | (24,0) | 0,0041 |
| Chronic Respiratory failure, n (%) | 2 | (5,6) | 9 | (2,8) | 0,408 |
| COPD, n (%) | 4 | (11,1) | 34 | (10,6) | 0,9241 |
| SAS, n (%) | 0 | (0,0) | 22 | (6,9) | 0,0279 |
| Asthma, n (%) | 0 | (0,0) | 24 | (7,5) | 0,0214 |
| Smoking, n (%) | 4 | (11,1) | 23 | (7,2) | 0,4214 |
| Diabetes, n (%) | 7 | (19,4) | 56 | (17,4) | 0,768 |
| Cancer, n (%) | 14 | (38,9) | 48 | (15,0) | 0,0011 |
| Cognitive disorders, n (%) | 10 | (27,8) | 20 | (6,2) | 0,0002 |
| Stroke n (%) | 9 | (25,0) | 13 | (4,0) | <0,0001 |
| <i>Imaging</i> | | | | | |
| Thoracic CT scan, n (%) | 24 | (66,7) | 152 | (47,4) | |
| Thoracic angioscan, n (%) | 12 | (33,3) | 163 | (50,8) | |
| Lung parenchymal involvement, mean (SD) | 37,8 | (22,3) | 26,5 | (17,8) | 0,0006 |
| Pulmonary embolism detected, n (%) | 0 | (0,0) | 16 | (5,0) | 0,1223 |
| <i>Biology</i> | | | | | |
| Hemoglobin, mean (SD) | 12,3 | (2,52) | 13,3 | (1,57) | 0,0006 |
| Hematocrit, mean (SD) | 37,1 | (6,8) | 39,3 | (4,2) | 0,0079 |

| | | | | | |
|---|---------------|-----------|---------------|----------|-------------------|
| Leukocytes, mean (SD) | 10,5 | (17,0) | 6,3 | (3 ,0) | <0,0001 |
| Neutrophils, mean (SD) | 6,3 | (5,1) | 4,8 | (3,1) | 0,0143 |
| Lymphocytes, mean (SD) | 1,59 | (3,28) | 1,00 | (0,6) | 0,0037 |
| N/L Ratio, mean (SD) | 8,9 | (7,0) | 6,4 | (6,0) | 0,0186 |
| Eosinophils, mean (SD) | 0,02 | (0,05) | 0,03 | (0,07) | 0,7752 |
| Basophils, mean (SD) | 0,02 | (0,02) | 0,01 | (0,01) | 0,0197 |
| Platelets, mean (SD) | 189,0 | (87,2) | 207,7 | (88,9) | 0,2335 |
| PT, mean (SD) | 68,6 | (24,1) | 76,4 | (18,0) | 0,0179 |
| APTT ratio, mean (SD) | 1,64 | (1,47) | 1,29 | (0,33) | 0,0004 |
| Fibrinogen, mean (SD) | 4,78 | (1,54) | 5,00 | (1,38) | 0,4144 |
| D-dimer, mean (SD) | 2311,0 | (2266) | 1187,7 | (1473,9) | 0,0002 |
| Natremia, mean (SD) | 136,2 | (6,05) | 135,6 | (3,84) | 0,3648 |
| Kalemia, mean (SD) | 4,2 | (0,7) | 3,9 | (0,42) | 0,0002 |
| Chloremia, mean (SD) | 99,7 | (5,64) | 98,9 | (3,94) | 0,2458 |
| Protidemia, mean (SD) | 69,4 | (7,8) | 71,0 | (5,3) | 0,0835 |
| Uremia, mean (SD) | 11,38 | (6,55) | 6,77 | (3,63) | <0,0001 |
| Creatininemia, mean (SD) | 127,1 | (85,9) | 90,1 | (42,0) | <0,0001 |
| Blood glucose, mean (SD) | 1,5 | (0,48) | 1,3 | (0,47) | 0,0113 |
| Calcemia, mean (SD) | 2,2 | (0,23) | 2,2 | (0,15) | 0,8117 |
| Phosphoremia, mean (SD) | 0,99 | (0,43) | 0,89 | (0,21) | 0,0576 |
| Magnesia, mean (SD) | 0,82 | (0,15) | 0,85 | (0,10) | 0,2291 |
| CKDEPI calculated, mean (SD) | 48,6 | (20,0) | 72,0 | (21,2) | <0,0001 |
| ASAT, mean (SD) | 49,0 | (32,5) | 46,8 | (28,7) | 0,6708 |
| ALAT, mean (SD) | 26,7 | (23,2) | 36,4 | (30,9) | 0,0783 |
| GGT, mean (SD) | 71,8 | (60,7) | 73,5 | (88,4) | 0,9124 |
| Lipase, mean (SD) | 45,6 | (32,4) | 50,8 | (48,5) | 0,6287 |
| Troponin, mean (SD) | 0,070 | (0,08) | 0,017 | (0,02) | <0,0001 |
| NT-pro-BNP, mean (SD) | 8770,7 | (18763,1) | 909,9 | (2599,7) | <0,0001 |
| CRP, mean (SD) | 98,0 | (76,4) | 65,9 | (55,4) | 0,0017 |
| PCT, mean (SD) | 0,6 | (1,21) | 0,2 | (0,48) | 0,0004 |
| LDH, mean (SD) | 464,1 | (207,0) | 308,4 | (84,0) | 0,0003 |
| <i>Pre Hospital therapies</i> | | | | | |
| Prehospital Antibiotic therapy, n (%) | 7 | (19,4) | 75 | (23,4) | 0,5896 |
| Prehospital Corticosteroid /NSAID, n (%) | 2 | (5,6) | 54 | (16,8) | 0,0483 |
| <i>Degree of independence</i> | | | | | |
| Autonomous, n (%) | 7 | (19,4) | 251 | (78,2) | <0,0001 |
| Assisted, n (%) | 14 | (38,9) | 46 | (14,3) | |
| Dependent, n (%) | 11 | (30,6) | 20 | (6,2) | |
| Bedriden, n (%) | 4 | (11,1) | 3 | (0,9) | |
| <i>Vital constants at emergency</i> | | | | | |
| Respiratory Rate, mean (SD) | 26,1 | (6,4) | 22,5 | (6,14) | 0,0088 |
| SpO2, mean (SD) | 89,4 | (6,9) | 93,4 | (4,5) | <0,0001 |
| Oxygenotherapy, mean (SD) | 0,5 | (1,58) | 0,07 | (0,42) | 0,0004 |

| | | | | | |
|--|--------------|----------------|--------------|----------------|-------------------|
| Systolic Blood Pressure, mean (SD) | 134,6 | (32,5) | 141,6 | (25,1) | 0,1491 |
| Diastolic Blood Pressure, mean (SD) | 75,5 | (18,3) | 78,2 | (13,8) | 0,3012 |
| Heart Rate, mean (SD) | 93,8 | (21,6) | 87,2 | (16,8) | 0,0373 |
| Temperature, mean (SD) | 37,6 | (0,88) | 37,5 | (0,87) | 0,6724 |
| <i>Vital constants on arrival in the pneumo-covid unit</i> | | | | | |
| Respiratory Rate, mean (SD) | 24,0 | (5,4) | 20,8 | (4,3) | 0,0001 |
| SpO2, mean (SD) | 94,5 | (2,5) | 95,6 | (2,0) | 0,0013 |
| Oxygenotherapy, mean (SD) | 3,5 | (3,2) | 1,6 | (2,0) | <0,0001 |
| Systolic Blood Pressure, mean (SD) | 132,4 | (22,3) | 130,4 | (21,3) | 0,6059 |
| Diastolic Blood Pressure, mean (SD) | 74,2 | (13,8) | 74,6 | (11,4) | 0,8376 |
| Heart Rate, mean (SD) | 86,6 | (17,4) | 81,1 | (13,5) | 0,0244 |
| Temperature, mean (SD) | 37,2 | (0,77) | 37,2 | (0,81) | 0,9304 |
| <i>Initial signs</i> | | | | | |
| Asthenia/malaise, n (%) | 28 | (77,78) | 275 | (85,67) | 0,2324 |
| Cough, n (%) | 17 | (47,22) | 220 | (68,54) | 0,0125 |
| Headache, n (%) | 7 | (19,44) | 87 | (27,10) | 0,3086 |
| Dyspnea, n (%) | 23 | (63,89) | 192 | (59,81) | 0,6339 |
| Myalgia, n (%) | 3 | (8,33) | 62 | (19,31) | 0,0786 |
| Digestive Signs, n (%) | 6 | (16,67) | 100 | (31,15) | 0,058 |
| Fever, n (%) | 20 | (55,56) | 198 | (61,68) | 0,4776 |
| Anosmia/Agueusia, n (%) | 2 | (5,56) | 68 | (21,18) | 0,0114 |

Table 4 - Multivariate analyses

4a – Transfer to Intensive Care Unit ; model with phosphorus and age-adjusted GFR

| Model Variables | OR | CI 95 % | p |
|--|--------------|-------------------------|---------------|
| Age cl 50-59 years vs lower 50 years | 1,015 | [0,2 ; 5,147] | 0,7619 |
| Age cl 60-69 years vs lower 50 years | 1,517 | [0,297 ; 7,75] | |
| Age cl 70-79 years vs lower 50 years | 1,93 | [0,369 ; 10,09] | |
| Age cl 80-89 years vs lower 50 years | 0,992 | [0,132 ; 7,436] | |
| Age cl 90+ years vs lower 50 years | 0,718 | [0,046 ; 11,209] | |
| F vs M gender | 0,285 | [0,117 ; 0,692] | 0,0056 |
| Parenchymal Lung Involvement (/ 10%) | 1,218 | [0,926 ; 1,603] | 0,1585 |
| Emergency SpO2 cl 90-95% vs sup or eq. 95% | 2,842 | [1,059 ; 7,629] | 0,003 |
| Emergency SpO2 cl inf. 90% vs sup or eq. 95% | 7,537 | [2,361 ; 24,065] | |
| High Blood Pressure | 0,943 | [0,377 ; 2,357] | 0,8997 |
| Diabetes | 0,923 | [0,327 ; 2,604] | 0,8793 |
| Cancer | 1,016 | [0,338 ; 3,056] | 0,9774 |
| Obesity | 2,095 | [0,826 ; 5,31] | 0,1191 |
| Cardiovascular Comorbidities | 2,228 | [0,849 ; 5,852] | 0,1038 |
| COPD and Chronic respiratory failure | 1,068 | [0,333 ; 3,426] | 0,9114 |
| Eosinopenia 1 vs 0 | 3,166 | [1,005 ; 9,975] | 0,0491 |
| Platelets (/ 50 000/mm ³) | 0,799 | [0,582 ; 1,096] | 0,1645 |
| Phosphoremia (/ 0,2mmol/L) | 0,691 | [0,471 ; 1,013] | 0,0583 |
| GFR CKDEPI (/ 20mg/L) | 0,587 | [0,326 ; 1,055] | 0,075 |
| CRP (/50mg/L) | 0,907 | [0,584 ; 1,408] | 0,6626 |
| Neutrophils (/ 1000/mm ³) | 1,074 | [0,907 ; 1,273] | 0,4081 |
| ASAT (/ 20UI/L) | 0,993 | [0,775 ; 1,273] | 0,9568 |
| PCT 0,1ng/mL) | 1,08 | [0,93 ; 1,253] | 0,3139 |

4b – Mortality; model without phosphorus and with age-adjusted GFR

| Model Variables | OR | CI 95 % | p |
|--|--------------|-------------------------|---------------|
| Age (/ 10 years) | 3,45 | [1,51 ; 7,884] | 0,0033 |
| F vs M gender | 2,013 | [0,535 ; 7,577] | 0,3011 |
| Parenchymal Lung Involvement cl 40+% vs lower 40% | 3,955 | [1,044 ; 14,982] | 0,043 |
| Emergency SpO2 cl 90-95% vs sup or eq. 95% | 8,736 | [1,455 ; 52,435] | 0,0575 |
| Emergency SpO2 cl inf. 90% vs sup or eq. 95% | 5,765 | [0,933 ; 35,611] | |
| High Blood Pressure | 0,398 | [0,112 ; 1,409] | 0,153 |
| Diabetes | 0,395 | [0,092 ; 1,689] | 0,2103 |
| Cancer | 3,584 | [0,879 ; 14,604] | 0,075 |
| Obesity | 0,213 | [0,02 ; 2,281] | 0,2012 |
| Cardiovascular Comorbidities | 1,217 | [0,361 ; 4,102] | 0,751 |
| COPD and Chronic respiratory failure | 0,842 | [0,16 ; 4,438] | 0,8397 |
| NTproBNP (/ 500) | 1,033 | [0,993 ; 1,075] | 0,1073 |
| Platelets (/ 50 000/mm3) | 0,574 | [0,36 ; 0,915] | 0,0195 |
| GFR CKDEPI (/ 20ml/min) | 1,586 | [0,679 ; 3,704] | 0,2866 |
| CRP (50mg/L) | 1,755 | [0,955 ; 3,228] | 0,0703 |
| PCT (/ 0,1ng/mL) | 1,082 | [0,993 ; 1,18] | 0,0731 |
| Hemoglobin (/1g/dL) | 0,686 | [0,457 ; 1,03] | 0,0693 |
| Neutrophils/Lymphocytes Ratio (/1) | 0,973 | [0,868 ; 1,091] | 0,6424 |
| Basophils (/ 0,01G/L) | 1,297 | [0,875 ; 1,922] | 0,1949 |
| Eosinopénia 1 vs 0 | 4 | [0,44 ; 36,349] | 0,2183 |
| Ddimer 1000ng/mL) | 1,2 | [0,898 ; 1,604] | 0,2174 |
| Kalemia (/ 1mmoL/L) | 4,14 | [1,275 ; 13,441] | 0,0181 |

4c – Mortality: model with phosphorus and age-adjusted GFR

| Model Variables | OR | IC 95 % | p |
|---|--------------|-------------------------|---------------|
| Age (/ 10 years) | 4,064 | [1,42 ; 11,631] | 0,009 |
| F vs M gender | 1,224 | [0,204 ; 7,343] | 0,8248 |
| Parenchymal Lung Involvement cl 40+% vs lower 40% | 4,459 | [0,832 ; 23,895] | 0,0809 |
| Emergency SpO2 cl 90-95% vs sup or eq. 95% | 11,005 | [0,834 ; 145,267] | 0,1554 |
| Emergency SpO2 cl inf. 90% vs sup or eq. 95% | 4,034 | [0,248 ; 65,67] | |
| High Blood Pressure | 0,153 | [0,024 ; 0,966] | 0,0458 |
| Diabetes | 0,615 | [0,093 ; 4,089] | 0,6154 |
| Cancer | 2,411 | [0,334 ; 17,409] | 0,383 |
| Obesity | 0,204 | [0,011 ; 3,916] | 0,292 |
| Cardiovascular Comorbidities | 1,593 | [0,3 ; 8,469] | 0,5847 |
| COPD and Chronic respiratory failure | 0,165 | [0,012 ; 2,195] | 0,1722 |
| NTproBNP (/ 500) | 1,05 | [0,996 ; 1,106] | 0,0723 |
| Platelets (/ 50 000/mm3) | 0,459 | [0,246 ; 0,86] | 0,015 |
| GFR CKDEPI (/ 20ml/min) | 1,374 | [0,457 ; 4,133] | 0,5714 |
| CRP (/ 50mg/L) | 3,51 | [1,311 ; 9,396] | 0,0125 |
| PCT (/0,1ng/mL) | 1,268 | [0,924 ; 1,74] | 0,1409 |
| Neutrophils/Lymphocytes Ratio (/1) | 0,459 | [0,23 ; 0,915] | 0,027 |
| Basophils (/ 0,01G/L) | 0,876 | [0,729 ; 1,052] | 0,1571 |
| Eosinopénia 1 vs 0 | 1,693 | [0,983 ; 2,915] | 0,0578 |
| Ddimer 1000ng/mL) | 10,412 | [0,527 ; 205,794] | 0,1238 |
| Kalemia (/ 1mmoL/L) | 1,216 | [0,845 ; 1,748] | 0,292 |
| Neutrophils/Lymphocytes Ratio (/1) | 4,765 | [1,023 ; 22,201] | 0,0467 |
| Phosphoremia (/ 0,2mmol/L) | 0,507 | [0,214 ; 1,202] | 0,1228 |

Discussion

The description at admission of the characteristics of the patients transferred to the intensive care unit included in this study reveals results in univariate analysis in line with what has been previously described in the medical literature. As a reminder, these were patients hospitalised for moderate COVID-19 for whom we were looking for the susceptibility to worsening in order to optimise their course of care. After multivariate analysis by a logistic regression system considering the confounding factors, we observe in this series that being male, having eosinopenia and an abnormal saturation (lower than 95%) in ambient air in the emergency room are the elements significantly associated with an increased risk of being transferred to the intensive care unit after admission to the COVID unit. Lowered phosphorus levels and glomerular filtration rate appear to describe a trend. In univariate analysis we report few associated comorbidities (age, peripheral arterial disease and high blood pressure). Biologically, the inflammatory markers were increased with impaired renal function and increased cardiac markers. Desaturation completes the picture of multi-organ damage. The lowered saturation as the scannographic damage in this case appears quite tautological. On arrival in the pneumo-COVID unit for a saturation target of 95% in the absence of any significant difference in pneumological history, patients transferred to the intensive care unit reveal a haematosiis that is more difficult to balance with an increased respiratory rate and a higher oxygen flow.

The originality of the results lies in the eosinopenia, eosinophils which are not the most mentioned leukocyte cells, far behind the lymphopenia and the emerging neutrophil/lymphocyte ratio. The second original feature is the trend towards lower phosphorus levels in patients progressing to a critical form.

Eosinophils

Initially recognised as a powerful diagnostic aid (18, 19, 20, 21, 22), eosinopenia also became a prognostic marker in the studies by Krishnamurthy et al, Du et al or Huang et al among others (23,24,25). Cazzaniga et al (26) in Italy report that patients with absolute eosinopenia have a higher risk of requiring intensive care (49.3% vs. 13.3%, $p<0.001$), and of dying (30.6% vs. 6.2%, $p=0.006$) compared to other patients, independtly of other leukocyte lineages. This contrasts with a meta-analysis by Lippi and Henry in 2020 which, despite a small volume of data, found no association of eosinopenia with adverse progression of COVID-19 (27). Some see a protective effect of eosinophilia (28, 29, 30).

Eosinopenia was first described by Zappert et al in 1893 in response to systemic inflammation. There was no distinction between viral and bacterial infection in adults. Nevertheless, it is a reliable marker of sepsis on admission to critical care (31) and restoration of its level is a good indicator of improved infection status (28, 32, 33). Conversely, persistent eosinopenia is associated with adverse outcomes in ARDS and sepsis (34, 35);

In COVID-19 the mechanism of eosinopenia is unclear, but several causes including inhibition of eosinopoiesis, inflammatory-induced apoptosis, reduced expression of certain receptors, and depletion of IL5-producing CD8+ T cells that contribute to eosinophil proliferation have been suggested (36). Among their functions, the anti-viral action of eosinophils has been suggested via direct cytotoxicity of their granulations and their ability to present antigens stimulating a specific immune response (37, 38, 39, 40). They also play an important immunoregulatory role (41,42, 43, 44). This second role seems the most crucial. Indeed, patients suffering from pathologies involving hypereosinophilia (asthma, Churg-Strauss syndrome...) and benefiting from anti-eosinophil therapy by monoclonal inhibition of interleukin 5 receptors (Benralizumab, Mepolizumab or Reslizumab) do not have a significantly increased risk of susceptibility to viruses (45). Case reports of patients treated with Benralizumab do not appear to show increased severity of SARS-CoV-2 infection (46, 47). Data from Cortés-Vieyra et al indicate that when eosinophils increase, cellular inflammatory markers decrease and vice versa. Eosinophils therefore seem to play a role in protecting against exacerbated inflammation and thus reduce organ damage. (28) They also increase phagocytic clearance and the recruitment of elements for tissue repair. (48) In their analysis of inflammatory markers, mediators and genes, viral load and cytology of blood and bronchoalveolar washings, Kim DM et al mention in their article that patients suffering from non-severe forms of the disease have a lower viral load and an early and rapid bronchopulmonary action of eosinophils in the first ten days, in contrast to severe forms in which eosinophils appear in a delayed and prolonged manner, with an imbalanced inflammatory reaction in favor of the type 1. (49). This type 1 inflammation results from the release of cytokines such as interferon γ or interleukin 12 that will activate adaptive immunity. It is characterised by high levels of IL 6, IL 8, IL1 and TNF α . It is known to participate in acute respiratory distress syndrome via a pro-inflammatory cascade, intense phagocytosis and tissue destruction. (50) In contrast, the type 2 reaction is characterised by activation of eosinophils in response to non-phagocytic extracellular organisms. It also allows the recruitment of myofibroblasts and activates angiogenesis, thus counterbalancing the so-called type 1 reaction. (51) Most critical forms of SARS-CoV-2 infection are explained by a phenomenon of hyperinflammation due to an excess of cytokines (IFN γ , IL1B IL6 IL12 IL17 TNF α and C3 and C5 complements) otherwise known as the "cytokine storm" induced by the

wide activation of leukocytes and epithelial cells which release large quantities of them. (52, 53)

In contrast to benign forms where the potential presence of a pulmonary resident eosinophil population and an early recruitment for antiviral and regulatory action would come into play, the absence of eosinophils in severe forms could therefore reflect a late and dysregulated recruitment of eosinophils for their cytotoxic role generating tissue damage through the generation of an oxidative environment and the release of their granulations, all in the absence of a type 2 reaction (54). In addition, corticosteroids used to balance the cytokine storm phenomenon cause a decrease in eosinophils. (55, 56). Finally, it has been noted that eosinopenia seems to be correlated with lymphopenia (57). All in all, eosinopenia can explain its role in the hyperactivation of the type 1 inflammatory response responsible for the critical forms of COVID-19 and validate its pejorative predictive value highlighted in this study.

Phosphorus

Phosphorus appears in our study to be a limiting factor (p 0.0583) with a multivariate OR of 0.691 (95% CI: 0.471 - 1.013), and therefore an option to explore. Indeed, Ruoran Wang et al describe hypophosphatemia as a risk factor for mortality in 33 patients with COVID-19 in a cohort of 453 in China (58), as did Xue et al in 32 patients. (59) This phenomenon has also been reported in several studies in intensive care patients with severe pneumonia (60, 61, 62, 63).

Phosphorus is an essential element for all organisms, entering into the structural composition of nucleic acids, membrane phospholipids, numerous energy mechanisms (ATP, glycolysis, erythrocyte 2,3-biphosphoglyceric acid, etc.) and cellular communication. Hypophosphataemia, although rare in the general population, is more frequently found in patients hospitalised in intensive care. The various recognized causes of hypophosphataemia are ketoacidosis, acute alcoholisation, severe burns, certain diuretics, undernutrition, severe respiratory alkalosis, theophylline intoxication, hypomagnesaemia and chronic hyperparathyroidism, vitamin D deficiency, malabsorption and hypothyroidism. (64, 65) Its consequences are varied. Altering the energy mechanisms, hypophosphatemia can be associated with a decrease in cardiac contractility that can lead to cardiac insufficiency and a decrease in diaphragmatic contractility. In sepsis, it is associated with an increased risk of death and leukocyte dysfunction (phagocytosis). (66) The role of phosphorus in the immune system is still very much debated; there is a positive relationship with hypophosphoremia and an inversion of the CD4/CD8 ratio of lymphocytes (58, 59); note the action of cytokines (IL 6

and TNF alpha in particular) which act on an intra-cellular transfer of phosphorus in order to meet the high ATP requirements of activated immune cells (59, 67)

However, the consequences on cellular energy metabolism contribute to organic dysfunctions (cardiac, renal, pulmonary...) and increase the affinity of haemoglobin for oxygen and thus a lesser release in peripheral tissues due to a decrease of 2,3-bisphosphoglycerate (2,3-BPG) increasing hypoxia. (68) Energy deficiency and hypoxia promote necrosis and apoptosis feeding the inflammatory response. On the other hand, hypophosphatemia alters insulin secretion by pancreatic beta cells due to lack of ATP and is associated with peripheral resistance to insulin action also altering cellular metabolism. Hyperglycemia reduces renal resorption in the proximal tubule of phosphorus (69, 70). Finally, the protective effect of vitamin D in COVID-19 has been demonstrated due to an immunomodulatory effect (71, 72). A study of a family with a genetic disease with a mutated vitamin D receptor (present on the membrane of antigen presenting cells) did not reveal any leukocyte difference in relation to SARS-CoV-2 (73). This leaves a possible uninvestigated interconnection between vitamin D, phosphorus homeostasis and metabolism.

One limitation is that studies on phosphorus involve small numbers and often show correlations with co-morbidities (high age, obesity, male sex, diabetes). There is significant intra-individual daily variation (up to 40%; minimum in the morning and maximum at night) which is not considered. Similarly, respiratory alkalosis related to hyperventilation (74) should be studied.

As for the PAD, it is found in the literature to be at high risk of mortality and complications (increased by 40% in the study by Smolderen et al, twice as high in the metanalysis by Zuin et al) and above all reveals a terrain comprising numerous concomitant comorbidities (75, 76, 77).

Mortality

In the second part of the study on mortality, thrombocytopenia and kalemia were significantly associated with an increased risk in multivariate analysis. The first is known from the medical literature and the cause is thought to be multifactorial (78, 79): on the one hand, the state of hyperinflammation generating a state of hypercoagulability which is a source of platelet consumption; on the other hand, bone marrow damage with a decrease in thrombopoiesis. SARS-CoV-2-related liver damage is also a hypothesis. (80) As for abnormalities of kalemia, its increase or hyperkalemia is according to several studies associated with increased mortality (81). The etiology here is also multifactorial, the first being direct renal damage by SARS-CoV-2 on the ACE2 receptor of the renal cells. (82) Uncontrolled hyperglycemia is also a credible

hypothesis. (83) Finally, renal tubular acidosis characterised type IV by hyperkalaemia and hyperchloremia may result from a reduction in sensitivity to aldosterone involving the renin angiotensin system, of which ACE2 receptors are a part, and from heparin toxicity. (84).

The early administration of corticosteroids, although not recommended before the 6th day according to the original DISCOVERY study, and the English referent authorities (NIH) (85) at the origin of the recommendations applied is a discordant result in our study;

Strength and limitations

The retrospective nature of the study, the declarative nature of the data (symptoms, smoking, etc.) and certain missing data are the limitations of this study. Indeed, smoking is usually estimated at 25-30% in the general population compared to 7.5% in the cohort studied, which raises an information bias. The emergence of several variants, variable health restrictions and the phasing in of the first vaccine doses that occurred during this study are not considered.

Vitamin D testing or gasometry could have provided additional information to support these results. The presence of seven patients on immunosuppressants is also an unaddressed issue.

The power of this study is the size of the population and a reflection of real practice conditions

Conclusion

The main risk factors for progression to a severe form described in the literature and found in our study frequently coexist because of a multiple comorbid terrain. These data can allow the clinician in current practice and at an early stage, even in the face of sometimes frustrating pictures, to adjust his or her management in the way that is best adapted to the patient's benefit. The originality of our results underlies several phenomena that seem to be interrelated and that should be explored to better understand this pathology and its severe forms.

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Appendix 1 – Bibliography : introduction – review of meta-analysis

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Serment d'Hippocrate

Au moment d'être admis(e) à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions.

J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité.

Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences.

Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis(e) dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçu(e) à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré(e) et méprisé(e) si j'y manque.

Abstract

Background: COVID19 is a multi-systemic disease resulting in both asymptomatic forms and respiratory distress. While facing the outbreak constraining our health care system, identify characteristics associated with adverse prognosis (transfer to intensive care unit and death) was required for an optimal clinical management and resource allocation in each population.

Material and method: This single-center observational study conducted at the Princess Grasse Hospital Center in the Principality of Monaco from September 1, 2020, to April 14, 2021, compares demographic, clinical, and biological characteristics at admission in the pneumo-COVID unit of patients who progressed secondarily to resuscitation (excluding LATA), and of patients who died.

Results: Among the 332 patients included, 76 were transferred to the ICU. Predictive factors for severe form were: age (p0.0063), male sex (p0.0029), hypertension (p0.0102), PAD (p0.0318), parenchymal involvement on CT (p0.0025), neutrophils (p0.0241), eosinophils (p0.0406), platelets (p0.0061), urea (p0.0120) creatinine (p0.0274), blood glucose (p0.0012), phosphorus (p0.0067), AST (p0.0303), CRP (p<0.001), PCT (p<0.0001), SpO2 in the emergency room (p<0, 001) SPO2 on admission to COVID unit (p0.0004), respiratory rate on the ward (p0.0229) dyspnea (p0.0004) and absence of anosmia (p0.0182). In multivariate analysis, male sex (p0.0056), eosinopenia (p0.0491) and emergency department SpO2 (p0.0030) remained significantly associated with the admission to the ICU. The multivariate analysis of patients who died identified age (p0.0033), platelets (p0.0195), parenchymal involvement on CT scan (p0.043) and kalemia (p0.0181) as risk factors for this cohort.

Conclusion: The clinico-biological data highlighted in this cohort are a tool to help the clinician in his management. Moreover, the underlying mechanisms are as many leads as possible for the understanding of the disease, and the improvement of care.

Keywords: SARSCoV-2, Monaco, ICU admission, severe form, prognostic factors