# Hyponatremia is Associated with Poor Outcome in COVID-19

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## Abstract

# Background

Hyponatremia has been described in severe acute respiratory syndrome. Our objective was to describe the impact of hyponatremia on COVID-19 patients' outcome (intensive care unit [ICU] admission, mechanic ventilation or death).

# Methods

According to natremia at admission, two groups were retrospectively screened: hyponatremic (< 135 mM, n = 101) or normonatremic (natremia ≥ 135 mM, n = 222) patients. Pearson's chi-2 (qualitative variables) and Student tests (quantitative variables) were used to compare the two groups. A multiple logistic regression model was used to assess the association of outcome and patients' data.

# Results

Hyponatremia was generally mild. There were more male patients in the hyponatremic group (p = 0.005). Pulmonary lesions on the first thoracic CT-scanner performed during the hospitalization were significantly more extended in the hyponatremic group (p = 0.03). ICU admission, mechanic ventilation or death were significantly higher in hyponatremic compared to normonatremic patients (34 versus 14%; p < 0.001; 16% versus 5%; p = 0.002; 19 versus 9%, p = 0.021, respectively). Hyponatremia was an independent predictor of poor outcome (adjusted Odds-ratio: 2.49 [1.18–5.33, p = 0.017]).

# Conclusions

Our study showed an independent relationship between hyponatremia at admission and transfer to ICU, use of mechanic ventilation or death in COVID-19. Hyponatremia may reflect the potential severity of underlying pulmonary lesions. Our results support the use of natremia as a simple bedside screening tool for early identification of SARS-CoV-2 infected patients at high risk of poor outcome.

## Background

As SARS-CoV-2 infection spread worldwide, the search for prognostic factors is essential to provide adapted care and improve patient survival. Obesity, age, gender or acute kidney failure have been reported as prognostic factors (1–3), such as lymphocytes counts (4), C-Reactive protein (5), troponin (6) or D-dimer (7). Hyponatremia has previously been described in severe acute respiratory syndrome (SARS). This condition occurred in one third of the SARS CoV 1 infected patients and was associated with poor prognostic (8,9). Our objective was to describe the impact of hyponatremia on COVID-19 patients' outcome (intensive care unit [ICU] admission, use of mechanic ventilation or death).

# Methods

We carried out a retrospective study on 329 adult patients admitted in Nantes hospital from February the 1st to May the 7th 2020 with a final diagnosis of COVID-19. Diagnosis was confirmed by a positive reverse transcription-PCR (RT-PCR) on nasopharyngeal swab (298 patients) or specific COVID-19 pattern (i.e. lung linear opacities, “crazy paving”) (10) on thoracic CT-scanner (31 patients). Ages under 18-year old, hypernatremia and previous hospitalization for COVID-19 were exclusion criteria. Blood sodium concentration was measured within 24 hours from the COVID-19 suspicion (assessed by the nasopharyngeal RT-PCR), by indirect potentiometry on plasma. Hyponatremia was defined by natremia below 135 mM. Epidemiological, demographic, clinical, laboratory and outcome data were extracted from electronic health records using a standard data collection form. Extracted data included demographic data, time between symptoms onset and hospital admission and known comorbidities (diabetes, obesity, congestive heart failure, coronary artery disease, cirrhosis, active neoplasia, current smoker and obesity defined by a body mass index $\geq 30$ kg/m$^2$). Vital parameters (tympanic temperature, systolic and diastolic blood pressure, respiratory rate, oxygen flow rate) and biological data (serum creatinine, lymphocytes count, fibrinogen, Alanine transaminase [ALT], Aspartate transaminase [AST], Troponin T hs, Creatine Kinase, C-Reactive protein) performed during the first 24 hours were extracted. Oxygen saturation (SpO2) was not extracted as it was often recorded after the initiation of the oxygenotherapy. Subjective symptoms were retrospectively screened with a significant number of missing values. Reports of the first CT-scanner performed during the hospitalization, focusing on the extension of specific COVID-19 lesions were also extracted. Patients may have had CT-scanner for several purposes: i) to assess the gravity of COVID-19, ii) to look for associated diagnosis (i.e pulmonary embolism or bacterial pneumonia), iii) to assess the COVID-19 diagnosis in case of a negative nasopharyngeal swab RT-PCR. Previous blood sodium concentrations from the same laboratory, during the twelve months preceding COVID-19 were retrospectively extracted for hyponatremic patients.

Results were expressed as proportions with 95% confidence interval, mean with standard deviation or median with 25th -75th percentile. Pearson’s chi-2 test (or alternative Exact test) was used for qualitative variables and Student test (or alternative Wilcoxon test) for quantitative variables to compare the two groups (hyponatremic and normonatremic patients). Chi-2 $>$ 3.84 and p value $<$ 0.05 were considered statistically significant. A multiple logistic regression model was used to assess the association of outcome and patients data after withdrawing variables with more than 20% of missing values (subjective symptoms, obesity, CT-scanner, Creatine Kinase, C-Reactive Protein, Troponin T hs, fibrinogen, D-dimer). Variables included in the model were selected if p value was $<$ 0.2 in univariate logistic regression model, excepted for serum creatinine and lymphocytes count, forced in the model as already described as independent prognostic factors (2,4). The local ethical committee approved the study (GNEDS April the 23rd 2020).

# Results

Hyponatremia is common in COVID-19's patients and associated with biological risk factors of poor outcome.

According to natremia at admission, two groups of patients were isolated: hyponatremic (natremia < 135 mM, n = 101, 31% of the cohort) and normonatremic (natremia ≥ 135 mM, n = 222) patients. Six patients with hypernatremia were excluded. Hyponatremia was generally mild (mean of natremia in the hyponatremic group 132.3 mM ± 1.7 [123–134]). Only 12 patients had a natremia below 130 mM. 30 on 101 hyponatremic patients (30%) had natremia measurement in the same laboratory during the year preceding COVID-19 and only 10 were found previously hyponatremic.

Plasmatic osmolality was rarely measured in our non-interventional retrospective cohort of mild hyponatremia (12 patients), and mostly after intravenous fluid administration. Thus, we unfortunately did not have consistent plasmatic osmolality data. To note, only 3 out of 12 samples were below 280-mOsm/kg/$H_2O$. On 34 urinary sodium measurements at admission in the hyponatremic patients, 15 (44%) had a < 30 mM natriuresis, which may suggest an extracellular dehydration state. Systolic blood pressure at admission and digestive symptoms (diarrhea, vomiting) were not significantly different between hyponatremic and normonatremic groups (Table 1). Neurologic symptoms (headache, confusion) previously described in COVID (11,12) were also not significantly different between groups at admission (Table 1).

Age and time between symptoms and hospital admission were similar between hyponatremic and normonatremic patients (Table 1). There were significantly more male patients in the hyponatremic group (p = 0.005). The major comorbidities classically associated with hyponatremia (cirrhosis, active neoplasia), and obesity were not different between groups. Surprisingly, more patients in the normonatremic group had a history of congestive heart failure (p = 0.031) (Table 1).

We looked for available prognostic factors in our cohort. Temperature at admission was significantly higher in hyponatremic patients (p < 0.001). Respectively 58 out of 93 (62%) patients and 83 out of 193 (43%) had a temperature above 38.5 °C in hyponatremic and normonatremic patients (Pearson Chi-squared test p = 0.003), which indicates a strong and significant correlation between high temperature and hyponatremia. At admission, serum creatinine and lymphocytes counts, were similar between the two groups (Table 2). C-Reactive protein was significantly higher in hyponatremic patients (p = 0.04) with a non-negligible number of missing values (32% in hyponatremic versus 22% in normonatremic group) (Table 2). AST and ALT were also significantly higher in hyponatremic patients (respectively p = 0.001 and 0.03) (Table 2).

Hyponatremia in COVID-19 is significantly associated with a poor outcome.

ICU admission, mechanic ventilation or death, were significantly higher in hyponatremic compared to normonatremic patients (respectively 34 versus 14%; p < 0.001; 16% versus 5%; p = 0.002; 19 versus 9%, p = 0.021) (Table 1).

We performed a multivariate analysis with available variables of interest (known as prognostic factor and/or with a p value < 0.2 in univariate analysis in the association with the primary outcome): age, sex, tympanic temperature, diabetes, serum creatinine, ALT, lymphocytes count and oxygen flow rate at admission (Table 3). Due to significant correlation with ALT associated with more missing values, AST was not included in the model. Respiratory rate and oxygen flow rate divided in three categories (none, ≤ 6 l/min, > 6 l/min) were also strongly associated (Kruskal Wallis test, p = 8.5e-09). Moreover, respiratory rate was not available in 61 patients (19% of the cohort). Thus, this parameter was not included, as we could not exclude that a missing value suggest an evaluation of lower severity at the admission of the patient. In multivariate analysis, hyponatremia at admission was an independent predictor of poor outcome (adjusted Odds-ratio: 2.49 [1.18–5.33, p = 0.017]) such as an oxygen flow rate above 6 l/min (adjusted Odds-ratio: 18.83 [6.32–64.30, p < 0.001]) (Table 3). Tympanic temperature, significantly higher in hyponatremic group was not an independent predictor of poor outcome in our cohort (adjusted Odds-ratio: 2.07 [0.96–4.58, p = 0.065] (Table 3).

Hyponatremia in SARS-CoV-2 infection may reflect severity of pulmonary lesions

As hyponatremia had already been described as a prognostic factor in SARS pulmonary infection and pneumonia (13), we assessed if hyponatremia was the consequence of severe pulmonary lesions in COVID-19. Oxygen flow at admission was not different between hyponatremic and normonatremic patients (Table 1). Mean oxygen flow rate in the patients with moderate oxygen flow rate (≤ 6 l/min) were also not significantly different (Table 1). We compared pulmonary lesions between hyponatremic and normonatremic patients (Table 2). 147 patients of our cohort had a pulmonary assessment with a CT-scanner. Pulmonary lesions on the first thoracic CT-scanner performed during the hospitalization were significantly more extended in the hyponatremic compared to the normonatremic group (Pearson Chi-squared test, p = 0.03) (Table 2) and extension of the lesions above 50% of the lungs was associated with poor outcome in univariate analysis (Odds-Ratio 18.86 [6.65–60.74, p < 0.001]) (Table 3).

# Discussion

Several prognostic factors have been reported in COVID-19, either clinical for most of them, or biological. Although hyponatremia is common in larger cohorts of COVID-19 (14), to our knowledge, its prognostic value has only been studied recently on a cohort of 29 patients, showing that hyponatremia may be associated with a poor outcome (15). Mild hyponatremia, occurring in a third of our cohort of 323 infected patients and more frequently in male, appeared to be associated with a poor outcome in COVID-19 (ICU admission, mechanic ventilation or death). Our results support the previous finding in SARS COV 1 infection (8), in COVID-19.

Physiopathology of hyponatremia in COVID-19 needs to be assessed. Two third of our hyponatremic patients with a natremia value obtained in the twelve months before COVID-19 (30/101 patients) were previously normonatremic. Underlying chronic hyponatremia may induce susceptibility for a poor outcome in COVID-19 but our data are suggestive of acute hyponatremia as a symptom of COVID-19.

Hyponatremia may reflect an extracellular dehydration state, induced by digestive symptoms, as suggested by the low natriuresis found in almost half of urinary sodium measurement. Syndrome of antidiuresis (SIAD) caused by lung parenchyma involvement may also be hypothesized. As SIAD itself has been associated with bacterial pneumonia and SARS, it will need to be determined if hyponatremia reflects the potential severity of underlying pulmonary lesions, and thereby, be associated with a poor outcome. This is consistent with the more severe lesions on CT-scanner in hyponatremic patients. Interestingly, the association of hyponatremia and poor outcome was maintained even after correction for oxygen flow rate at admission in multivariate analysis.

Our retrospective study could not include the numerous prognostic factors in COVID-19, which emerged from worldwide studies. Moreover, despite a significant number of patients in these previously published cohorts, natremia was never considered as a prognostic factor. We believe that, as a difference with the other biological prognostic factors, hyponatremia should be considered as a state and not as a quantitative assessment. Indeed, natremia is tightly regulated by contrast to the other biological prognostic factors (i.e lymphocytes count, C-Reactive Protein, D-Dimer…). The disruption of this regulation may be associated with the poor outcome in COVID-19. Temperature above 38°5 C at admission was also associated with a poor outcome in our cohort. We studied this variable, already described as a prognostic factor in COVID-19 (16,17), and especially as hyponatremia may be associated with fever. We found significant association between these two variables, but after multivariate analysis, only hyponatremia remains an independent risk factor.

# Conclusion

To conclude, identification of prognostic factors in COVID-19 remains essential to provide adapted care and discuss associated medication administration. In 323 patients with COVID-19, our study showed an independent relationship between hyponatremia at admission and transfer to ICU, use of mechanic ventilation or death. Our results support the use of natremia in hospitalized COVID-19 patients as another bedside screening tool for early identification of patients at high risk of poor outcome. Larger cohorts and experimental studies may precise physiopathology of hyponatremia in COVID-19.

# Declarations

*Ethics approval and consent to participate:

This retroscpective study has been approved by the local ethical committee (GNEDS)

*Availability of data and material:

on request

*Competing interest:

None

*Funding:

None

*Authors' Contributions:

Research idea and study design: HDC, NG, LF; data acquisition: HDC, TL, MK, GD, HC, EP, MBL, NB, NG, LF; data analysis/interpretation: HDC, TL, NG, LF; statistical analysis: HDC, MK, LF; supervision or mentorship: NG, LF; writing and revision of the manuscript: HDC, TL, MK, HC, EC, GC, PL, EM, AR, NG, LF. Each author contributed important intellectual content during manuscript drafting or revision, accepts personal accountability for the author's own contributions, and agrees to ensure that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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# Tables

Table 1:
Characteristics and outcome of the two groups of patients (hyponatremic or normonatremic at admission)

| | Missing values (n(%) | Hyponatremic (n = 101) | Missing values (n(%) | Normonatremic (n= 222) | p |
|---|---|---|---|---|---|
| Age – y ± SD | 0 | 67 ± 16 | 0 | 69 ± 18 | 0.227 |
| Male (n/%) | 0 | 67 (66) | 0 | 108 (49) | **0.005** |
| Time between symptoms and admission – days* ± IQR | 0 | 6 [3-9] | 0 | 5 [1-10] | 0.203 |
| **Comorbidities** | | | | | |
| Diabetes (n/%) | 0 | 19 (19) | 0 | 36 (16) | 0.678 |
| Obesity (n/%) | 20 (20) | 21/80 (26) | 63 (28) | 32/159 (20) | 0.390 |
| Congestive heart failure (n/%) | 0 | 5 (5) | 0 | 29 (13) | **0.031** |
| Coronary artery disease (n/%) | 0 | 16 (16) | 0 | 34 (15) | 1.000 |
| Cirrhosis (n/%) | 0 | 2 (2) | 0 | 4 (2) | 1.000 |
| Active neoplasia (n/%) | 0 | 7 (7) | 0 | 14 (6) | 1.000 |
| Current smoker (n/%) | 0 | 11 (11) | 0 | 16 (7) | 0.372 |
| **Vital signs** | | | | | |
| Body temperature (°C)<br>*Temperature > 38.5* | 8 (8) | 38.8 ± 0.9<br>*58/93 (62)* | 29 (13) | 38.4 ± 0.9<br>*83/193 (43)* | **< 0.001**<br>***0.003*** |
| Systolic blood pressure (mmHg) | 5 (5) | 149 ± 18 | 8 (4) | 149 ± 22 | 0.792 |
| Diastolic blood pressure (mmHg) | 5 (5) | 84 ± 11 | 8 (4) | 86 ± 11 | 0.296 |
| Respiratory rate (/min) | 20 (20) | 30 ± 8 | 52 (23) | 28 ± 7 | **0.015** |
| **Symptoms** | | | | | |
| Diarrhea (n/%) | 0 | 29 (29) | 5 (2) | 67 (31) | 0.879 |
| Vomiting (n/%) | 0 | 10 (10) | 5 (2) | 19 (9) | 0.862 |
| Agueusia (n/total n, %) | 27 (27) | 21/74 (28) | 74 (33) | 38/148 (26) | 0.788 |
| Anosmia (n/total n, %) | 27 (27) | 21/74 (28) | 76 (34) | 31/146 (21) | 0.312 |
| Neurologic involvement (n/%) | 0 | 16 (16) | 7 (3) | 24 (11) | 0.308 |

| | | | | | |
|---|---|---|---|---|---|
| **Oxygenotherapy** | | | | | |
| Oxygenotherapy | 3 (3) | | 10 (4) | | |
| No oxygenotherapy (n/total n, %) | | 51/98 (51) | | 127/212 (60) | 0.293 |
| Oxygenotherapy ≤ 6 l/min (n/total n, %) | | 34/98 (36) | | 67/212 (31) | |
| *Mean oxygen flow – l/min ± SD* | | *3.3 ± 1.0*[£] | | *3.0 ± 1.3*[£] | |
| Oxygenotherapy > 6 l/min (n/total n, %) | | 13/98 (13) | | 18/212 (9) | |
| **Outcome** | | | | | |
| Total Poor outcome | 0 | 40 (40) | 0 | 46 (21) | **0.001** |
| Transfer in ICU (n/%) | 0 | 34 (34) | 0 | 31 (14) | **< 0.001** |
| Mechanic ventilation (n/%) | 0 | 16 (16) | 0 | 11 (5) | **0.002** |
| Death (n/%) | 0 | 19 (19) | 0 | 20 (9) | **0.021** |

*Main clinical symptoms and comorbidities of the patients are detailed. Body mass index was not available in all patients, such as subjective symptoms (missing values are indicated). Oxygen flow rate was classified in three groups (no oxygenotherapy, ≤ 6 l/min, > 6 l/min).*

*Results are expressed with mean ± standard deviation (SD) or median [Interval Quartile Range] for quantitative variable and comparability between groups was evaluated with Student or non-parametric Wilcoxon test (*). P value is indicated for each test (p < 0.05 was considered as significant).*

*Results are expressed with number of patients/percentage for qualitative variables and comparability between groups was evaluated with Pearson's Chi-squared test with chi-2 > 3.84 considerer as significant.*
*[£]Not significant (p = 0.300)*

Table 2:
Biological parameters at admission and CT-scanner report in the two groups of patients (hyponatremic or normonatremic)

| | Missing values N (%) | Hyponatremic (n = 101) | Missing values N (%) | Normonatremic (n= 222) | p |
|---|---|---|---|---|---|
| **Biological parameters** | | | | | |
| Creatinine (µM) | 0 (0) | 88 ± 38 | 1 (0.5) | 91 ± 46 | 0.511 |
| Lymphocytes counts* (x$10^9$ /l) | 3 (3) | 0.88 [0.62-1.18] | 12 (5) | 0.96 [0.71-1.45] | 0.122 |
| ALT* (UI/l) | 21 (21) | 35 [23-70] | 34 (15) | 30 [20-46] | **0.031** |
| AST* (UI/l) | 21 (21) | 53 [41-81] | 36 (16) | 38 [26-55] | **< 0.001** |
| Fibrinogen* (g/l) | 52 (52) | 5.0 [4.2-7.4] | 110 (49) | 4.7 [4.1-6.5] | 0.149 |
| C-Reactive protein* (mg/l) | 32 (32) | 72 [34-136] | 49 (22) | 42 [13-95] | **0.04** |
| Troponin* (ng/l) | 34 (34) | 12 [8-26] | 92 (41) | 17 [9-37] | 0.104 |
| Creatine Kinase* (UI/l) | 44 (44) | 126 [64-301] | 104 (47) | 94 [52-211] | 0.182 |
| D-dimer* (ng/ml) | 71 (71) | 716 [420-1261] | 157 (71) | 654 [445-1065] | 0.710 |
| **CT-scanner** | | | | | |
| Thoracic CT-scanner performed (n/%) | 52 (52) | | 95 (43) | | |
| CT-scanner: < 30 % lesion (n/total n, %) | | 11/54 (20) | | 40/93 (44) | 0.030 |
| CT-scanner: 30-50 % lesion (n/total n, %) | | 24/54 (45) | | 36/93 (36) | |
| CT-scanner: > 50 % lesion (n/total n, %) | | 17/54 (35) | | 19/93 (20) | |

*Main biological parameters at admission including known prognostic markers and extension of SARS CoV-2 lesions on CT-scanner are detailed. Extension of lesions was classified in three groups (< 30 %, 30-50 %, > 50 %). Missing values are indicated.*

*Results are expressed with mean ± standard deviation (SD) or median [Intervalle Quartile Range] for quantitative variable and comparability between groups was evaluated with Student or non parametric Wilcoxon test (*). P value is indicated for each test (p < 0.05 was considered as significant).*

*Results are expressed with number of patients/percentage for qualitative variables and comparability between groups was evaluated with Pearson's Chi-squared test with chi-2 > 3.84 considerer as significant.*

Table 3:
Univariable and multivariable Logistic Regression for poor outcome

| | Missing values (%) | OR (univariable) | OR (multivariable) |
|---|---|---|---|
| Hyponatremia | 0 | 2.49 (1.49-4.18, p < 0.001) | **2.49 (1.18-5.33, p = 0.017)** |
| Age | 0 | 0.99 (0.98-1.00, p = 0.175) | 1.01 (0.99-1.04, p = 0.277) |
| Male | 0 | 1.74 (1.05-2.92, p = 0.032) | 1.43 (0.67-3.09, p = 0.357) |
| Diabetes | 0 | 1.63 (0.86-3.01, p = 0.125) | 2.30 (0.98-5.37, p = 0.054) |
| Temperature | 11.5 | 2.35 (1.69-3.35, p < 0.001) | N/A |
| Temperature > 38.5°C | | 2.93 (1.66-5.32, p < 0.001) | 2.07 (0.96-4.58, p = 0.065) |
| Oxygenotherapy | 4 | | |
| None | | | |
| ≤ 6 l/min | | 1.56 (0.85-2.85, p = 0.150) | 1.42 (0.65-3.10, p = 0.370) |
| > 6 l/min | | 20.56 (8.23-59.35, p < 0.001) | **18.83 (6.32-64.30, p < 0.001)** |
| Creatinine* | 0.3 | 1.00 (1.00-1.01, p = 0.358) | 0.82 (0.30-2.14, p = 0.695) |
| ALT* | 17.7 | 1.01 (1.00-1.01, p = 0.026) | 1.52 (0.91-2.53, p = 0.106) |
| Lymphocytes count* | 4.6 | 1.05 (0.98-1.14, p = 0.204) | 1.57 (0.95-2.68, p = 0.082) |
| | | | |
| Time between symptoms and admission | 0 | 1.01 (0.96-1.05, p = 0.810) | |
| Obesity | 25.7 | 1.88 (0.95-3.64, p = 0.064) | |
| Congestive heart failure | 0 | 0.83 (0.34-1.83, p = 0.658) | |
| Coronary artery disease | 0 | 0.76 (0.36-1.53, p = 0.465) | |
| Cirrhosis | 0 | 2.81 (0.51-15.43, p = | |

| | | |
|---|---|---|
| | | 0.212) |
| Active neoplasia | 0 | 0.85 (0.27-2.25, p = 0.756) |
| Current smoker | 0 | 1.70 (0.72-3.81, p = 0.209) |
| Diarrhea | 2.2 | 1.05 (0.60-1.80, p = 0.862) |
| Vomiting | 2.2 | 1.13 (0.45-2.58, p = 0.776) |
| Agueusia | 31.3 | 0.44 (0.17-0.99, p = 0.063) |
| Anosmia | 31.9 | 0.53 (0.20-1.20, p = 0.152) |
| Systolic blood pressure | 4.0 | 1.01 (1.00-1.02, p = 0.204) |
| Diastolic blood pressure | 4.3 | 1.01 (0.99-1.03, p = 0.363) |
| Respiratory rate | 22 | 1.13 (1.08-1.18, p < 0.001) |
| Neurologic involvement | 2.5 | 1.63 (0.79-3.26, p = 0.174) |
| CT-scanner:<br>< 30 %<br>30-50 % lesion<br>> 50 % lesion | 54.5 | <br><br>1.78 (0.66-5.11, p = 0.264)<br>18.86 (6.65-60.74, p < 0.001) |
| AST | 17.0 | 1.00 (1.00-1.01, p = 0.099) |
| Fibrinogen | 50.2 | 1.23 (1.03-1.48, p = 0.026) |
| Troponin | 39.0 | 1.00 (1.00-1.01, p = 0.111) |
| Creatine Kinase | 45.8 | 1.00 (1.00-1.00, p = 0.460) |
| C-Reactive Protein | 25.1 | 1.01 (1.01-1.02, p < 0.001) |

*Odds-Ratio (OR) were calculated by univariable and multivariable not weighted logistic regression models. Subjective symptoms and variables with an excess of missing values (i.e > 20 %) were withdrawn for the multivariable analysis. Due to strong correlation with oxygen flow rate and the number of missing values, respiratory rate was not included in the multivariate analysis.*

**Creatinine, lymphocytes count and ALT were included in the model as natural logarithmic transformation.*

*N/A : not applicable*