Hypocapnia as a predictor of the need for non-invasive mechanical ventilation in subjects with SARS-CoV-2 related pneumonia

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Abstract

SARS-CoV-2 related pneumonia is characterized by moderate- to severe hypoxemia often associated with hypocapnia the prognostic role of which is poorely documented. Our aim in the present study was to evaluate if hypocapnia can predict the need for Non-Invasive Mechanical Ventilation (NIMV) in this setting. We prospectively studied 52 subjects with moderate-severe SARS-CoV-2 related pneumonia. All the following data were collected at admission to the Emergency Department and processed by unuvariate and multivariate analysis: clinical and laboratory data, blood gas analysis in room air and lung ultrasound. A total of 33 out of 52 subjects (63.4%) underwent NIMV. At univariate analysis PaCO2 was inversely associated to the need for NIMV (OR 0.82, CI 95% 0.689-0.976, p 0.025). At multivariate analysis PaCO2 predicted the need for NIMV independently from age, gender, number of comorbidities, d-dimer, CRP, PaO2 and LUS SCORE (OR 0.838, CI 95% 0.710-0.988, p .035). Our data suggest that hypocapnia could be an early predictor of clinical worsening in these patients independently from other known predictors of unfavourable outcome, reflecting the occurrence of a deep and frequent respiratory pattern possibly related to the generation of excessive transpulmonary pressure swings leading to a Self-Induced Lung Injury (P-SILI). Further studies are needed for validating these data on greater populations.

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Introduction

About 3 years passed but Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) pandemic is still not ended. Although the situation is ameliorated, mainly after vaccine introduction, more than 6 millions people died worldwide so far.[1] Also, as a consequence of the continuous appearance of novel variants able to elude immune system protection induced by both vaccines and acute infection, the global incidence of new cases and mortality in fragile subjects are still high.[1] In these years many papers concerning the risk stratification of covid patients have been published and some systematic review and meta-analysis are also available.[2-4] Unfortunately, all these systematic review and meta-analysis showed that the proposed models are at elevated risk of bias and have low performance, mainly because of high heterogeneity and lack of prospective design.[2-4] Moreover, many of these studies are based on scoring systems already used for other diseases or focused their attention on generic parameters common to other diseases, such as epidemiological data (age, gender), number and type of comorbidities, laboratory data including inflammation index, D-Dimer, serum lactic dehydrogenase, creatinine, glomerular filtration rate, haemoglobin levels and platelets count, thus being not specific for SARS-CoV-2 related disease; only few studies focused their attention on respiratory parameters and the most common used was the PaO2/FiO2 ratio.[2-4]

The clinical spectrum of Coronavirus Disease 19 (COVID-19) can range from asymptomatic infection to severe pneumonia with acute respiratory distress syndrome and death.[5] It is well known that one of the major characteristics of SARS-CoV-2 related pneumonia is the presence of a moderate to severe hypoxemia not associated to proportional clinical signs of respiratory distress.[6] Almost always hypoxemia is associated with hypocapnia. Covid pneumonia is characterized by an initial phase of prevalent interstitial and microvascular involvement, which leads to a condition of altered microvascular regulation and diffuse alveolar damage and, at least

in the first phase, lung compliance is not significantly compromised; thus, the patient develops a respiratory pattern characterized by greater depth of breaths and greater respiratory frequency without feeling the respiratory effort and with consequent hypocapnia development.[7]

To our knowledge only few previous studies directly or indirectly evaluated the potential role of hypocapnia as a predictor of respiratory failure worsening in subjects with SARS-CoV-2 related pneumonia.

We aimed our study for evaluating if hypocapnia detected at the time of admission to the Emergency Department could predict the need for Non-Invasive Mechanical Ventilation (NIMV) in subjects with SARS-CoV-2 related pneumonia.

Materials and Methods

We prospectively conducted our study at the field hospital set up near the emergency department of our hospital to accommodate SARS-CoV-2 infected patients in the time period between March and June 2021. Data collection has been interrupted because of changes in SARS-CoV-2 pandemic epidemiology (the end of the pandemic wave) which caused a change in the function of our subintensive unit thus not allowing the enrollment of new cases.

The end-point of the study was the need for Non-Invasive Mechanical Ventilation (NIMV).

Predefined criteria for considering the escalation of respiratory support to NIMV were the presence of SpO2 ≤92% while on VMK or HFNC or PaO2/FiO2 ratio ≤180 mm Hg with FiO2 ≥50%, and at least one between respiratory rate ≥28 breaths/min, severe dyspnea, signs of increased work of breathing (e.g., use of accessory muscles). All the data (clinical medical history, vital signs, laboratory parameters, blood gas analysis and lung ultrasound) were obtained at the time of admission to the emergency room.

In order to eliminate the possible confounding effect of the supplemental oxygen administered, all blood gas analysis were performed in room air. After blood gas analysis oxygen was administered using Venturi-Mask (VMK) or High Flow Nasal Canula (HFNC) according to clinical judgement.

Eligibility criteria were: age ≥18 years old; positive PCR test confirming SARS-CoV-2 infection; clinical signs of acute respiratory infection and radiological or ultrasound evidence of pneumonia; peripheral oxygen saturation (SpO2) ≤92% or arterial partial pressure of oxygen to fraction of inspired oxygen (arterial oxygen tension (PaO2)/FiO2) ratio <300 in room air and need for oxygen therapy according to clinical judgement, at screening. Exclusion criteria included: respiratory rate ≥28 breaths/min; PaO_2/FiO_2 ratio ≤200; need for immediate intubation or for NIMV according to clinical judgement; patients already on NIMV at study screening; septic shock; evidence of multiorgan failure; Glasgow Coma Scale <13; neuromuscular disease; presence of partial pressure of arterial carbon dioxide (PaCO2) >45 mm Hg or history of chronic hypercapnia. Patients already on long-term oxygen therapy and/ or home NIV/CPAP or with limitation of care based on patients' or physicians' decision or with the inability to comprehend the study content and give consent were also excluded. At admission we took note of the following comorbidities: Hypertension (HTN), diabetes, dyslipidaemia, obesity, Chronic Ischemic Cardiomyopathy (CIC), Cerebrovascular Disease (CVD), Peripheric Obliterative Arteriopathy (PAOD), Atrial Fibrillation (AF), Chronic Obstructive Pulmonary Disease (COPD); we reported the sum of them as Number Of Comorbidities (NOC).

The following laboratory parameters were included: White Blood Count (WBC) with its relative formula, Haemoglobin (Hb), Platelets (PTL), glycemia, urea, creatinine, Glomerular Filtration Rate (GFR; calculated with MDRD formula), INR, RATIO, d-dimer, Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), albumin, serum Lactic Dehydrogenase (LDH), C-Reactive Protein (CRP).

All patients underwent standard Lung Ultrasound (LUS) for calculating the LUS SCORE. LUS was performed using the standardized acquisition protocol which provides the acquisition of 12 standard areas (2 posterior, 2 lateral, and 2 anterior).[8] Images were acquired by 5 well experienced emergency physicians using a convex probe with a frequency of 1-6 Hz (W-Cube i7, Alpinion). For each area the severity of lung findings was described numerically as follows: score 0: the pleural line is continuous and regular and presence of A-lines; score 1: the pleural line is indented and presence of at least 3 well-spaced B-lines; score 2: presence of coalescent B-lines or presence of the so-called "white lung" pattern; score 3: presence of consolidation. LUS SCORE was calculated by the sum of the highest scores obtained in each area.

The local Ethical Committee approved the study (approval number 3948/21). Written informed consent was obtained from all patients.

Statistical analysis

Given the small sample size we reported the data as median and range. We used Student's t test and the Mann-Whitney U test to compare parametric and non-parametric variables. For testing the univariate relations among variables we used binary logistic regression analysis and Spearman's rank correlation coefficients. Binary logistic regression was used for testing the effect of possible confounding factors on the considered end-point. Analyses were performed with SPSS software (version 19.0; SPSS, Inc., Chicago, IL), with statistical significance set at $p<0.05$.

Results

In the study period 52 patients, out of 282 admitted to the field hospital, fully met the inclusion criteria (30 males and 22 females); mean age was 61 ± 12 years. Mean number of comorbidities was 1,04 ± 1,03. The most frequent comorbidity was arterial hypertension, followed by dyslipidemia and obesity (see Figure 1). None of the subjects included was affected by CIC, CVD or PAOD. Only

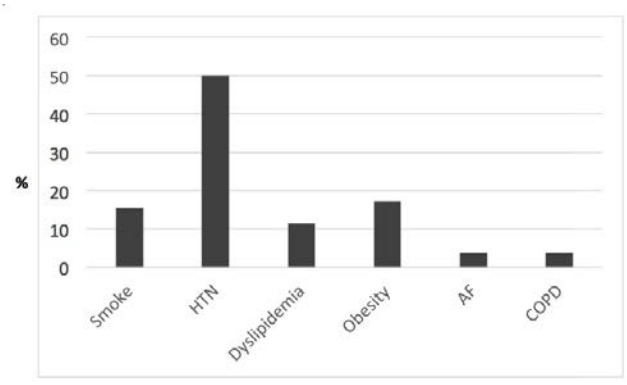

Figure 1. Percentage of the most frequent comorbidities in the population study

2/52 (3.8%) of the subjects included were affected by COPD; considering that we excluded from the study hypercapnic subjects it is not likely that the presence of COPD patients in our population altered the results. The other general characteristics of the population are described in Table 1.

In 21/52 subjects (40.3%) oxygen was administered using HFNC, in 31/52 (59.7%) oxygen was administered using Venturi-Mask (VMK).

33/52 of the subjects included (63.4%) reached the end point requiring NIMV. Mean time from admission to NIMV start was 20,3 ± 13 hours.

In Table 2 comparison between patients treated with VMK versus HFNC are shown. The differences of the general characteristics between patients who needed NIV and patients who did not are shown in Table 3.

Table 1. General characteristics of the population

	Median	Range
Age, years	61.5	36-89
Days from symptoms onset	7	0-15
Days from positive swab	6	0-15
SBP, mmHg	141.5	80-174
DBP, mmHg	82	45-103
HR, bpm	93	50-120
RR, breaths/min	26	14-36
Body Temperature, °C	36.7	35-38
WBC, 10^3/mm^3	7020	1140-14690
N, %	82.8	36.7-2.7
L, %	13.2	2.7-53.7
M, %	4.9	1-11.4
E, %	0.000	0.0-0.6
B, %	0.000	0.0-0.4
Hb, g/dl	13.7	10-18.6
PLT, 10^3/mm^3	185	91-361
Glycemia, mg/dl	133.5	92-315
Urea, mg/dl	38	13-110
Creatininemia, mg/dl	0.81	0.42-1.6
GFR, ml/min/1,73 m^2	93.1	41-116
D-dimer, µg/ml	676	224-5363
AST, UI/L	50	23-881
ALT, UI/L	43	13-480
Albumin mg/dl	3.6	2.9-4.5
LDH, UI/L	393	206-1476
CRP, mg/dl	7	1.6-326
LUS SCORE	12	0.0-36
Blood gas analysis		
pH	7.47	7.25-7.54
PaO_2	57.4	45.3-77.5
$PaCO_2$	30.8	17.7-42.7
HCO_3-, mEq/L	22.7	14-31
P/F	274.6	217-371

SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; RR: respiratory rate; WBC: white blood cells; N: neutrophils; L: lymphocyte; M: monocyte; E: eosinophils; B: basophils; Hb: haemoglobin; PTL: platelets; GFR: glomerular filtration rate; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: serum lactic dehydrogenase; CPK: creatine phosphokinase; CRP: C-reactive protein; LUS SCORE: Lung Ultrasound SCORE

At univariate analysis we found an inverse statistically significant association between $PaCO_2$ and need for NIMV. On the contrary we did not find any significant association between need for NIMV and age, gender, number of comorbidities, systolic or diastolic blood pressure, heart rate, respiratory rate, white blood cells count, neutrophils, lymphocyte, platelets, blood urea, creatinine, glomerular filtration rate, AST, ALT, D-dimer, LDH, CRP, PaO_2 and LUS SCORE (Table 4).

We did not find any significant association between $PaCO_2$ and respiratory rate (rho -0,257, p 0.075) and between $PaCO_2$ and LUS SCORE (rho -0.060, p 0.679).

The oxygen delivery system used (VMK or HFNC) was not significantly associated with the need for NIMV (OR 0.571, IC 95% 0.178-1.832, p .346).

At multivariate analysis $PaCO_2$ levels were able to predict the need for NIMV independently from age, gender, number of comorbidities, D-dimer, CRP, PaO_2 and LUS SCORE (OR 0.838, IC 95% 0.710-0.988, p .035; Table 5).

Discussion

Our results suggest that hypocapnia could be a good predictor of rapid respiratory failure worsening in subjects affected by SARS-CoV-2 related pneumonia independently from other already

Table 2. Comparison between patients treated with VMK versus HFNC

	VMK	HFNC	p
Age, yrs	65 ± 12	62 ± 14	ns
Days from symptoms onset	7.5 ± 3	7.2 ± 3	ns
Days from positive swab	5.8 ± 3	6.3 ± 3	ns
Number of comorbidities	1.2 ± 1.18	0.76 ± 0.7	ns
SBP, mmHg	139 ± 22	140 ± 14	ns
DBP, mmHg	80 ± 14	81 ± 10	ns
Heart rate, bpm	93 ± 16	86 ± 19	ns
Respiratory rate, breaths/min	25 ± 5	25 ± 4	ns
Body temperature, °C	36.8 ± 0.7	36.9 ± 08	ns
WBC, 10^3/mmc	7094 ± 2764	7829 ± 3512	ns
HB, mg/dL	14.3 ± 1.4	13.4 ± 1.8	ns
PTL, 10^3/mmc	193 ± 66	197 ± 59	ns
Glycemia, mg/dL	161 ± 60	137 ± 33	ns
Urea, mg/dL	42 ± 23	39 ± 12	ns
Creatinin, mg/dL	0.87 ± 0.26	0.81 ± 0.19	ns
GFR, mL/min/1,73 m^2	87 ± 21	88 ± 16	ns
D-dimer, µg/mL	710 ± 337	952 ± 1086	ns
AST, IU/L	75 ± 60	86 ± 182	ns
ALT, IU/L	67 ± 68	62 ± 99	ns
Albumin, mg/dL	3.6 ± 0.3	3.6 ± 0.3	ns
LDH, IU/L	412 ± 140	474 ± 260	ns
CRP, mg/mL	7.6 ± 4.4	26.7 ± 69	ns
pH	7.47 ± 0.04	7.47 ± 0.05	ns
PaO_2, mmHg	59 ± 6	57 ± 5	ns
$PaCO_2$, mmHg	31 ± 5	30 ± 4	ns
HCO_3-, mEq/L	23 ± 4	22 ± 3	ns
P/F	281 ± 28	272 ± 21	ns

known predictors. In our study $PaCO_2$ levels are the only parameter significantly associated to the need for NIMV also after correction for the main variables currently considered as severity disease predictors, whether they are patient pre-existing characteristics (age, gender, number of comorbidities), laboratory parameters (inflammation index and D-dimer) or ultrasound data (LUS SCORE), able to quantify the entity of lung involvement.

It is likely that hypocapnia is expression of one of the pathophysiological mechanisms involved in respiratory failure worsening of covid patients. SARS-CoV-2 related pneumonia follows always the same evolution phases that we can conceptually divide into phases based on the intensity of treatment required.[9] There is a first inflammatory phase without atelectasis which correspond to patient arrival to the emergency department. Subsequently, the disease can evolve to a phase characterized by edema and atelectasis which correspond to patient's admission to semi-intensive or intensive care unit and finally the disease can resolve or can evolve towards a fibrotic phase.[9] The first phase is characterized by a preserved lung compliance which allows for a respiratory pattern characterized by deep and frequent breathing.[9] The occurrence of this respiratory pattern that causes hypocapnia on one hand, can generate an excessive swing of transpulmonary pressures on the other hand, inducing a real risk of a patient self-induced lung injury (P-SILI),[10,11] thus maintaining a vicious circle that can promote the evolution to a more severe phase of the disease. Thus, we believe that the degree of hypocapnia detected at emergency department arrival help us in identifying those patients at higher risk of self-induced lung injury and thus at higher risk of rapid respiratory failure worsening. Surprisingly our data analysis shows that $PaCO_2$ levels are not associated with respiratory rate. Maybe in the first phase of SARS-CoV-2 related pneumonia the increase in respiratory depth is more pronounced than the increase in respiratory rate.

In our data also LUS SCORE is not significantly associated with $PaCO_2$ levels, suggesting that the degree of lung involvement does not influence the presence of hypocapnia.

In line with the results of COVID-HIGH trial,[12] the first multicenter randomized controlled trial to report results on the use of high-flow nasal oxygen in hospitalized patients with COVID-19 and mild hypoxemia, in our study the type of oxygen delivery system (VMK or HFNC) is not associated with the need for NIMV.

Table 3. Comparison between NIMV and non-NIMV patients.

	NO-NIMV	NIMV	p
Age, yrs	62 ± 11	60 ± 12	ns
Days from symptoms onset	7.2 ± 4	7.3 ± 2	ns
Days from positive swab	6.7 ± 3	5.5 ± 3	ns
Number of comorbidities	1 ± 0.9	1 ± 1	ns
SBP, mmHg	140 ± 21	140 ± 18	ns
DBP, mmHg	81 ± 13	80 ± 12	ns
Heart rate, bpm	86 ± 17	92 ± 17	ns
Respiratory rate, breaths/min	24 ± 3	25 ± 5	ns
Body temperature, °C	36.8 ± 0.8	36.8 ± 0.8	ns
WBC, 10^3/mmc	7475 ± 3571	7274 ± 2802	ns
HB, mg/dl	13.8 ± 1.2	14.1 ± 1.8	ns
PTL, 10^3/mmc	222 ± 75	184 ± 55	.045
Glycemia, mg/dl	135 ± 34	161 ± 57	.047
Urea, mg/dl	40 ± 12	42 ± 22	ns
Creatinin, mg/dl	0.84 ± 0.19	0.85 ± 0.25	ns
GFR, ml/min/1,73 m^2	87 ± 18	88 ± 20	ns
D-dimer, µg/ml	805 ± 413	806 ± 869	ns
AST, IU/L	50 ± 21	95 ± 152	ns
ALT, IU/L	52 ± 32	74 ± 98	ns
Albumin, mg/dl	3.6 ± 0.2	3.6 ± 0.3	ns
LDH, IU/L	369 ± 95	471 ± 232	ns
CRP, mg/ml	7 ± 5	20 ± 55	ns
pH	7.47 ± 0.04	7.47 ± 0.05	ns
PaO_2, mmHg	60 ± 7	58 ± 4	ns
$PaCO_2$, mmHg	32 ± 4	29 ± 5	.055
HCO_3-, mEq/L	24 ± 4	22 ± 3	.017
P/F	284 ± 34	274 ± 20	ns

Table 4. Univariate analysis among variables included in the study and need for NIMV

	OR	95% CI	p
Age	1.001	0.955 – 1.048	0.981
Gender	1.1196	0.387 – 3.697	0.756
Number of comorbidities	0.982	0.568 – 1.698	0.948
SBP	1.003	0.974 – 1.033	0.851
DBP	0.992	0.948 – 1.038	0.725
HR	1.029	0.993 – 1.065	0.112
RR	1.123	0.981 – 1.286	0.093
WBC	1.000	1.000 – 1.000	0.416
N	1.054	0.999 – 1.113	0.054
L	0.952	0.899 – 1.009	0.098
PLT	0.995	0.986 – 1.004	0.277
Urea	1.017	0.984 – 1.050	0.315
GFR	0.997	0.968 – 1.028	0.861
Creatininemia	1.664	0.142 -19.567	0.685
AST	1.015	0.993 – 1.037	0.197
ALT	1.006	0.995 – 1.017	0.297
D-dimer	1.000	0.999 – 1.001	0.843
LDH	1.003	0.998 – 1.007	0.227
CRP	1.106	0.988 – 1.239	0.079
PaO_2	0.899	0.799 – 1.011	0.076
$PaCO_2$	0.859	0.749 – 0.984	0.028
LUS SCORE	1.075	0.994-1.163	0.072

Table 5. Multivariate analysis among predictors of the need for NIMV

	OR	95% CI	p
Age	0.981	0.923-1.043	0.526
Gender	1.217	0.283-5.243	0.792
N° comorbidities	0.743	0.340-1.588	0.432
D-dimer	0.999	0.998 – 1.001	0.273
CRP	1.114	0.946 – 1.312	0.196
PaO_2	0.928	0.808-1.066	0.291
$PaCO_2$	0.838	0.710-0.988	0.035
LUS SCORE	1.062	0.963-1.171	0.228

To our knowledge only few previous studies explored the role of hypocapnia as a possible predictor of disease severity. Some studies indirectly explored the possible role of hypocapnia using the standard PaO_2, which corrects PaO_2 for $PaCO_2$ levels, for calculating the P/F ratio.[1,13] In the study by Prediletto et al, the authors showed that using the standard PaO_2 is more accurate than the traditional P/F in predicting in-hospital mortality,[13] while, on the contrary, Maraziti *et al.* showed that calculating the P/F ratio using the standard PaO_2 is not able to predict this outcome.[14] More directly a retrospective study on 165 covid subjects requiring NIMV showed that $PaCO_2$ levels are significantly lower in non-survivors.[15] Similarly, in a previous study we showed that the ratio between $PaCO_2$ levels and the fraction of inspired oxygen was able to predict the need for invasive mechanical ventilation independently from several already known predictors of severe disease.[16]

In line with these studies, that indirectly demonstrated the predictive role of clinical worsening of hypocapnia, our data prospectively highlight its potential role in predicting the need for NIMV in a patient population entering the emergency department for acute respiratory failure related to SARS-CoV-2 infection, independently of a number of confounding factors.

Another interesting aspect is that the mean time from admission to NIMV start was only about 20 hours. We suppose that hypocapnia allows the recognition of those subjects in which the pathophysiological mechanism causing the P-SILI is ongoing and thus allows the early recognition of those subjects at higher risk of early deterioration. This could also explain why we did not find significant association among the already known predictors of severe disease and the need for NIMV. It is likely that parameters such age, gender, comorbidities, inflammation and prothrombotic state are more efficient in predicting long-term outcomes, such as mortality or intubation, than a short-term outcome.

In conclusion our data suggest that hypocapnia seems to be a good predictor of the need for NIMV in subjects affected by SARS-CoV-2 related pneumonia, independently from other already known predictors of unfavorable outcome. Moreover, we observed that the majority of subjects needed NIMV support after few hours from admission suggesting that hypocapnia allows the early recognition of the subjects at higher risk of rapid deterioration. Certainly, a better risk stratification of covid patients, helping physicians in choosing the better allocation of covid patients is needed and certainly further multicentric studies are needed for validating these data.

Limitations

The main limitation of our study is the small simple size. Unfortunately changes in SARS-CoV-2 pandemic epidemiology at the time of data collection (the end of the pandemic wave) caused a change in the function of our sub-intensive unit thus not allowing the enrollment of new cases.

The study is monocentric and therefore the results may not be extensible to different contexts. This mean that the potential role of hypocapnia need an external validation.

Finally, we did not include in our analysis the Rox index, which was validated as a predictor of hospitalization and mortality of covid patients in the setting of the emergency department.[17] However ROX index is defined as the ratio of pulse oximetry/fraction of inspired oxygen (SpO_2/FiO_2) to Respiratory Rate (RR). We wanted to focus our attention on the role of hypocapnia for the possible pathophysiological role in identifying the subjects at higher risk of P-SILI and for eliminating the possible confounding effect of the supplemental oxygen we included in our study only subjects with blood gas analysis performed in room air. For this reason, we believe that calculating the ROX index in this contest could be at high risk of bias, without adding new information respect to the already existing data on ROX index in covid patient.

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