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Thematic Article

C-Reactive Protein and Partial Oxygen Pressure in the Peripheral Blood Predict Hospital Admission in Patients with Covid-19 Infection Observed in Emergency Department

Kostic Irena[1], Bonora Antonio[1]*, Olivato Alessia[2], Melchioretto Barbara[2], Zaccaria Eleonora[1] and Maccagnani Antonio[1]

[1]*Emergency and Intensive Care Department, University Hospital of Verona, Italy*

[2]*Postgraduate School of Emergency Medicine, University of Verona, Italy*

***Corresponding Author:** Bonora Antonio, Emergency and Intensive Care Department, Borgo Roma University Hospital, Verona, Italy.

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Abstract

Background: Coronavirus disease has been spreading around the world like a dramatic pandemic. The wide spectrum of clinical variability makes the identification of patients needing for timely hospitalization a crucial issue. Several studies have already assess the relationship between laboratory abnormalities and outcome in admitted patients, but none of these has been yet carried in acute setting.

Aim: The aim of this retrospective observational study was to investigate whether simple and easy to collect clinical and laboratory findings could have affected the admission in these patients.

Patients and Methods: We carried our study in the Emergency Department of the University of Verona (Italy) between 16th and 31st March 2020, considering all consecutive patients with SARS-CoV-2 detection by polymerase chain reaction in nasopharyngeal swab. Patients were then enrolled if fullfill one or more of these symptoms: fever equal or more than 38°, cough, shortness of breath, tachypnoea. In all patients accurate medical history wqs reported and blood gas analysis, laboratory examinations and chest x-rays were performed. After evaluation, physicians decided for patient discharge or admission. All discharge patients were followed until disease resolved without sequel.

Statistical analysis: Sensitivity, specifity, positive predictive value (PPV) and negative predictive value (NPV) were derived from the receiver operating characteristic (ROC) curves and analysed. The optimal cut-off values of biomarkers were established by ROC curves and cut-off values for each parameter affecting hospitalization were calculated from the areas under ROC curves (AUC). The groups were compared with Mann-Whitney test and proportion of patients with Chi-square test. Difference set at $p < 0.05$ was considered significant.

Results: Out of 190 positive for SARS-CoV-2, 109 symptomatic patients (69 males, 40 females; mean age 67 years, range 27 - 93) formed the study population. After ED evaluation, 86 patients (78.9%) were admitted, while 23 (21.1%) were discharged and then healed without sequel. The respective cut-off values of variables more significantly related with hospitalization were: age over 60 years, pO_2 less than 70 mmHg, SpO_2 less than 95%, CRP superior to 26 mg/l and positive chest x-rays ($p < 0.001$). We reported the higher hospitalization rate for pO_2 (167 times) and CRP (108 times) respectively. Age over 75 years and pO_2 less than 53 mmHg well predicted in-hospital death and ICU admission ($p = 0.001$).

Conclusion: Both pO_2 and CRP could be simple and reliable predictor of admission in COVID-19 patients, while age and pO_2 related with outcome.

Keywords: *COVID-19 Infection; Emergency Department; Hospital Admission Rate; Laboratory Parameters; Predictor Factors*

Abbreviations

COVID-19: Corona Virus Disease-19; SARS: Severe Acute Respiratory Syndrome; CoV-2: Corona Virus-2; ARDS: Acute Respiratory Distress Syndrome; ED: Emergency Department; RT-PCR: Reverse Transcript Polymerase Chain Reaction; Hb: Hemoglobin; Ht: Hematocrit; MCV: Mean Corpuscolar Volume; RDW: Red Cells Distribution Width; WBC: White Blood Cells Count; PLTS: Platelets; CRP: C-Reactive Protein; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; PPV: Positive Predictive Value; NPV: Negative Predictive Value; ROC: Receiver Operating Characteristic; AUC: Area Under the Curve; ICU: Intensive Care Unit; pO_2: Partial Oxygen Pressure; SpO_2: Percutaneous Oxygen Saturation; CI: Confidence Interval; CFR: Case Fatality Rate

Introduction

Corona virus disease 2019 (COVID-19), a form of respiratory and systemic zoonosis caused by novel highly contagious corona virus 2 (SARS-CoV-2), starting from the first epidemic outbreak in Wuhan, Popular Republic of China, has spreaded worldwide as an uncontrolled pandemic [1]. A wide spectrum of disease severity has been reported, ranging from asymptomatic patients to critical ones [1,2]. In over 15% of patients the clinical course is complicated by the onset of interstitial pneumonia, evolving toward acute respiratory distress syndrome (ARDS) [1-4]. Therefore, it is very important to identify which patients observed in Emergency Department (ED) should have a complicated course and then have to be admitted in order to prevent the risk of ARDS.

Several studies described laboratory abnormalities in patients with COVID-19, but almost all of them were carried in hospitalized patients [5-8]. In a recent meta-analysis the main laboratory abnormalities in patients with unfavorable course of COVID-19 were described [9]. Some of these laboratory parameters may be considered significant predictors of adverse clinical outcome and even death [10].

Aim of the Study

The aim of this study was to assess which laboratory findings reported in patients with COVID-19 at the ED admittance could have supported the hospital admission and then if they were related to the need for intensive care and mortality.

Patients and Methods

Patients: This retrospective observational study was performed in the Emergency Department of University Hospital of Verona between 16th and 31st of March 2020. All patients consecutively observed in the study period were considered eligible if confirmed cases according to Global Surveillance for COVID-19 [11]. The criteria for COVID-19 confirmation were the SARS-CoV-2 detection by reverse transcript polymerase chain reaction (RT-PCR) in nasopharyngeal and oropharyngeal swab; evidence of at least one of these symptoms: fever equal or more than 38°C, cough, shortness of breath, diarrhea or tachypnoea.

In all patients medical history, blood gas analysis and blood examinations were collected. The risk factors and underlying disease that could affect the course of COVID-19 were carefully recorded. All patients were submitted to chest X-rays and typical pulmonary findings, interstitial involvement and unilateral or bilateral infiltrates, accurately described.

Based on the clinical and instrumental evaluation, the patients were then admitted or discharged at home. All discharged patients were followed by our Department of Hygiene and Epidemiology and Family practitioners until the disease resolved without sequel.

This study was carried in accordance with the Declaration of Helsinki and after approval by our Ethics Committee.

Methods: Hematologic parameters, hemoglobin (Hb), hematocrit (Ht), mean corpuscular volume (MCV), red cell distribution width (RDW), white blood cell count (WBC) and differential formula (neutrophil and lymphocyte count) as well as platelets (PLTS) number, were determined using a SYSMECS XN9000 analyzer. The values of C-reactive protein (CRP), creatinine, glucose, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, sodium and potassium were calculated using a ROCHE COBAS analyzer. Blood gas analysis was performed using a PREMIER GEM 4000 analyzer (Werfen, USA).

Statistical analysis: *S*ensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated on the patients data. PPV and NPV were derived from the receiver operating characteristic (ROC) curves. In order to establish the optimal cut-off

values of biomarkers, ROC curves were designed and the area under the curve (AUC) determined. Cut-off values for each parameter likely to affect hospital admission were calculated from the AUC. Comparison among the groups was performed by the Mann-Whitney test and the proportions of patients were compared by the Chi-square test. A differences level of $p < 0.05$ was considered statistically significant.

Statistical analysis was carried using IBM SPSS Statistics (version 19, SPSS Inc., IBM Company, Chicago, IL, USA).

Results

Out of the 190 patients resulted positive for SARS-CoV-2, 109 patients (69 males, 40 females, mean age 67 years, range 27 - 93) were symptomatic and then enrolled in the study population. After the ED evaluation 84 patients (77.1%) needed for hospitalization while 25 (22.9%) were discharged and healed without sequel.

Two patients were transferred to other hospitals and then considered drop-out. Out of remaining 82 patients, 17 (20.7%) were admitted to Intensive Care Unit (ICU) while 65 (79.35) to dedicated departments.

Eighteen patients (21.9%) died within 7 days on average (range 2 - 40). The median hospital stay of 64 survived patients (78.1%) was 11.5 days (range 3 - 51), while 30 days (range 11 - 46) of those admitted to ICU (p = 0.0001). After discharge all patients were alive at 30 days follow-up.

In table 1 were summarized the features of all the enrolled patients.

Features	Discharged (25)	Hospitalized (84)	ICU (17)	Lethal outcome (18)	P value
Age, yrs, mean ± SD	50,9 ± 13,5	72,1 ± 13	63,9 ± 11,5	80,8 ± 8,4	0,001
Sex (male:female)	14:11	55:29	16:1	12:6	NS
Risk factors, (0 : 1 or more)	14: 10	22:62	7:10	4:14	0,002
Chest radiography (negative or interstitial pulmonary infiltrates)	15:9	8:76	0:17	1:17	0,001
Hb g/l, median (range)	147 (96 - 167)	139 (93 - 174)	148 (107 - 173)	137 (100 - 168)	NS
RDW, median (range)	12,5 (11,8 - 15,7)	13,2 (11,2 - 21,8)	13 (11,7 - 16,4)	14 (12,5 - 21,7)	0,05
WBC x 10^9/l, median (range)	3,8 (2,7 - 11,9)	6,8 (2,8 - 42)	7,1 (3,2 - 13,4)	7,2 (3,8 - 42)	0,001
Ne x 10^9/l, median (range)	2,4 (1,6 - 8)	5,4 (0,4 - 20)	5,7 (2,4 - 11,9)	4,9 (0,4 - 20)	0,001
Ly x 10^9/l, median (range)	1,2 (0,6 - 2,6)	1,05 (0,14 - 3,2)	1,03 (0,3 - 2,8)	1,2 (0,3 - 3,2)	NS
PLTS 10^9/l, median (range)	177 (95 - 451)	189,5 (71 - 471)	173 (87 - 433)	173 (121 - 435)	NS
CRP mg/l, median (range)	8,5 (1 - 73)	84 (3 - 336)	76 (23 - 336)	89 (4 - 273)	0,001
Creatinine µmol/l, median (range)	73 (53 - 112,6)	87,2 (46 - 291)	91 (55 - 146)	103 (46 - 291)	0,004
Sodium mmol/l, median (range)	139 (133 - 145)	138 (126 - 159)	135 (126 - 142)	138 (129 - 159)	NS
Potassium mmol/l, median (range)	4,15 (3,7 - 4,7)	3,9 (2,7 - 5,1)	3,9 (3,6 - 5,1)	4 (3,5 - 5)	NS
ALT units/l, median (range)	27 (13 - 54)	33,5 (8 - 195)	35 (8 - 92)	32 (8 - 195)	NS
SpO_2 %, median (range)	98 (96 - 99)	95 (73 - 99)	93 (74 - 98)	91 (73 - 98)	0,001
pO_2 mmHg, median (range)	79 (71 - 86)	59 (34 - 85)	52 (34 - 79)	52 (37 - 80)	0,001

Table 1: *Characteristics of COVID - 19 patients admitted at the Emergency Department.*
NS: Non Significant.

There was no difference between the groups regarding gender, apart from a male prevalence in patients requiring ICU admission. Discharged patients were significantly younger than the other groups, while deceased patients were the oldest ones (p = 0.001). We reported a prevalence of risk factors and underlying disease (p = 0.002), as well a significant elevation of hematologic parameters and

inflammatory markers in admitted than in discharged patients (p = 0.001). Also, the incidence of interstitial infiltrates was significantly superior in the former group of patients (p = 0.001). On the other hand, levels of partial oxygen pressure in the peripheral blood (pO_2) and percutaneous oxygen saturation (SpO_2) were significantly higher in the discharged than in admitted patients (p = 0.001).

Table 2 showed optimal cut-off values, sensitivity, specificity, PPV, NPV and diagnostic accuracy derived from ROC analysis for every single parameter that could predict hospital admission, need for ICU and death.

Variable		AUC (95% CI)	Cut-off	Sensitivity %	Specificity %	PPV %	NPV %	Accuracy %
Admission	Age	0,87 (0,78 - 0,97)	60 years	83,3	87,5	95,9	60	84,3
	Risk factors	0,71 (0,59 - 0,82)	1 or more	73,8	58,3	86,1	38,8	70,4
	Chest radiography	0,75 (0,6 - 0,9)	One infiltrate	90,5	62,5	89,4	65,2	84,3
	CRP	0,92 (0,87 - 0,98)	26 mg/l	90,5	83,3	95	71,4	88,9
	SpO_2	0,89 (0,82 - 0,94)	95%	58,3	100	100	40,7	65,7
	pO_2	0,93 (0,9 - 0,98)	70 mmHg	83,3	100	100	65,7	87
Intensive care unit	Age	0,74 (0,62 - 0,85)	75 years	88,2	60	36,6	95,1	65,8
	SpO_2	0,68 (0,54 - 0,8)	92 %	47,1	73,8	42	84,2	68,3
	pO_2	0,72 (0,58 - 0,85)	53 mmHg	58,8	75,4	38,5	87,5	72
Exitus	Age	0,78 (0,67 - 0,89)	78 years	77,8	71,9	43,8	92	73,2
	SpO_2	0,75 (0,61 - 0,88)	92 %	72,2	81,3	52	91,2	79,3
	pO_2	0,72 (0,58 - 0,85)	53 mmHg	61,1	76,7	42,3	87,5	73,2

Table 2: *AUC, cut-off, sensibility, specificity, positive predictive value (PPV) and negative predictive value (NPV) for variables predicting hospital recovery, ICU admission and lethal outcome.*

The respective cut-off values of the variables significantly related to hospitalization rate were: age over 60 years (95% CI 0.78 - 0.97, PPV 95.9%), pO_2 less than 70 mmHg (95% CI 0.90 - 0.98, PPV 100%), SO_2 less than 95% (95% CI 0.82 - 0.94, PPV 100%), CRP superior to 26 mg/l (95% CI 0.87 - 0.98, PPV 95%) and positive chest x-rays (95% CI 0.60 - 0.90, PPV 89.4%).

CRP and pO_2 were the most accurate predictor for hospital admission (binary logistic regression model F (2.108) = 73.6; R square = 0.49 - 0.76; p = 0.001), accounting a 108 and 167 times increase respectively. Patients older than 60 years were 35 times more likely to be admitted. Patients with SpO_2 less or equal than 95% 23 times higher probability of hospital admission. In addition, the presence of at least unilateral pulmonary infiltrate led to a risk of hospital admission 26 times higher than the patients with normal chest X-ray or only interstitial involvement.

Age over 75 years and pO_2 less than 53 mmHg well predicted in-hospital death (binary logistic regression model F (2.82) = 21.7; R square = 0.23 - 0.36; p = 0.001) as well as ICU admission (binary logistic regression model F (2.82) = 19.8; R square = 0.21 - 0.34; p = 0.001).

Discussion

The rapid and maybe unexpected spreading of COVID-19 pandemic in the Western countries did not allow to achieve an adequate knowledge of the disease and its early clinical manifestations [1,2]. Moreover, preliminary data derived from Chinese experience were mostly referred to inhospital patients [5-8]. Thus, emergency physicians of Northern Italy, the first European outbreak of infection, had suddenly and dramatically found themselves managing a high number of patients, often critically ill, not provided with reliable guidelines and decision rules.

In fact, the possibility of a rapid and unexpected worsening of clinical conditions in apparently stable individuals had required a careful assessment of which patients had to be admitted and which ones could be safely discharged. For this purpose, emergency physicians strongly needed a number of simple and reliable parameters supporting their clinical decision.

The University Hospital of Verona had been chosen as "hub" centre during the pandemic and then we observed and admitted either to ICU or dedicated departments a high number of patients with COVID-19 infection. Moreover, the lack of adequate clinical knowledge of the pandemic could have forced us to an excessive hospitalization rate. Therefore, we retrospectively evaluated the clinical and laboratory features of patients observed for COVID-19, both admitted and discharged, in order to assess the decision thresholds for hospital admission.

In this study we found that CRP and pO_2 in the peripheral blood were the best predictors of need for hospital admission in patients suffering to ED with COVID-19 infection.

Notably, pO_2 was more specific and sensitive than SpO_2 in identifying COVID-19 patients to be admitted and well correlated with the need for intensive care and the outcome. This result stressed the relevant role of pO_2, even in absence of evident dyspnea or desaturation, in promptly identifying the patients at risk of clinical worsening.

The role of CRP seemed more difficult to interpretate, since its elevation was typical of bacterial rather than viral infections and, mostly, specificity was lower than sensitivity. This is not unexpected because CRP levels could be influenced by the underlying diseases and tissue damage, all factors affecting its specificity [12]. Probably, high CRP levels reflected the activation of inflammatory mechanisms that could complicate and worsen the course of viral disease [7,16,18].

The higher hospitalization rate in older people is expected since the function of the lungs, the principal target of SARS-CoV-2 and also the tolerance to hypoxia gradually declines with increasing age. Furthermore, the incidence of chronic disease increases with aging. In our study 66% of the patients had at least one underlying disease before the COVID-19 onset and then had four times need for hospital admission.

Our results are consistent with other studies reporting that elderly, high number of comorbidities and prominent laboratory abnormalities were associated with more severe COVID-19 infection that required hospitalization [5,13-16]. Moreover, in a small series of younger patients (median age 49 years) mortality rate in presence of underlying disease was 15% [6]. These data were further corroborated in a largest Chinese study conducted so far on over 40,000 confirmed COVID-19 cases, in which the overall case fatality rate (CFR) was 2.3% and hypertension (CFR 6.0%), diabetes (CFR 7.3%), cardiovascular disease (CFR 10.5%) and age > 70 (CFR 10.2%) were the most frequently reported co-morbidities [2].

The older age trend of our admitted patients well correlated with mortality rate (Table 1). One could speculate that higher expression of angiotensin-converting enzyme 2 (ACE 2), known as SARS-CoV-2 receptors, in elderly people and in some comorbidities, like hypertension or cardiovascular disease, could reflect a more severe clinical presentation and need for hospital admission [16,17]. However, further studies are needed to confirm this hypothesis.

Instead, relationship between age and ICU admission rate was quite controversial. Older patients were certainly more candidates for intensive care, but those admitted to ICU were fairly younger patients with less comorbidities. The decision to exclude from intensive treatment the two older and less like to survive patients was a dramatic decision from the ethical point of view.

Biomarkers could be reliable predictors of progression from mild to severe disease and then enhance the quality of clinical care. In accordance with other studies, we found that increased CRP, WBC and neutrophil count might be an index of disease severity [10,13,14,17]. Furthermore, though less significant, also higher RDW levels were found to be related with hospitalization rate (Table 1). The harmful effect of SARS-CoV-2 on various tissues and organs is an important field of investigation [10,16-18]. However, SARS-CoV-2 is known to induce an inflammatory response in the organism and inflammation is probably the most frequent cause of anisocytosis as revealed by high RDW [19]. The exact mechanism of this viral or immune-induced damage should be investigated in future studies [7,16,18].

Finally, the typical characteristics of COVID-19 infection is the pulmonary involvement and the respiratory impairment related to high tropism of SARS-CoV-2 for the alveolar cells. Indeed, the presence of pulmonary infiltrate, at least unilateral increased the probability of hospital admission compared to patients with normal chest imaging or only interstitial involvement [15].

Our study is burdened by some limitations. Firstly, it is a single centre retrospective study carried in a short period of time, anyway representative of the most acute phase of COVID-19 pandemic in a widely involved area. Most of all, it was not easy to retrospectively assess the actual reason for hospital admission in each patient and the decision itself could have been influenced by several factors. Moreover, the evaluation of prognostic role of these parameters on the outcome was obviously hindered by the efficacy of therapies and the complications eventually arisen during hospital stay.

Despite these limitations, our study is a simple and real snapshot of COVID-19 patients at the time of ED admittance. Even if retrospectively assessed, our results could be an easy to collect and rapidly available decision-making tools for the admission of discharge of the patients. Moreover, they are expected to be useful in better managing a possible second wave of the COVID-19 pandemic.

Conclusion

CRP and pO_2 are reliable parameters that could support emergency physicians in rapidly deciding if patients with confirmed COVID-19 infection have to be admitted or should be safely discharged at home. Age and pO_2 itself are well related with the need for ICU admission and mortality and then could effectively identify the patients at higher risk of unfavorable outcome.

Bibliography

1. Zhou F., *et al.* "Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study". *Lancet* 20.6736 (2020).
2. WHO-China Joint Mission. "Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19), 2020".
3. World Health Organization. "Coronavirus disease 2019 (COVID-19). Situation report-43" (2020).
4. Mattiuzzi C and Lippi G. "Which lessons shall we learn from the 2019 novel coronavirus outbreak?" *Annals of Translational Medicine* 8.3 (2020): 48.
5. Zhang JJ., *et al.* "Clinical characteristics of 140 patients infected by SARS-CoV-2 in Wuhan, China". *Allergy* 19 (2020).
6. Huang C., *et al.* "Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China". *Lancet* 395.10223 (2020): 497-506.
7. Chen N., *et al.* "Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study". *Lancet* 395.10223 (2020): 507-513.
8. Xu XW., *et al.* "Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-CoV-2) outside of Wuhan, China: retrospective case series". *British Medical Journal* 368 (2020): m606.
9. Lippi G and Plebani M. "Laboratory abnormalities in patients with COVID-19 infection". *Clinical Chemistry and Laboratory Medicine* (2020).
10. Deng Y., *et al.* "Clinical characteristics of fatal and recovered cases of coronavirus disease 2019 (COVID-19) in Wuhan, China: a retrospective study". *Chinese Medical Journal* 20 (2020).
11. "Global Surveillance for COVID-19 caused by human infection with COVID-19 virus".
12. Santolaya ME., *et al.* "C-reactive protein: a valuable aid for the management of febrile children with cancer and neutropenia". *Clinical Infectious Diseases* 18 (1994): 589-595.

13. Chen G., *et al.* "Clinical and immunologic features in severe and moderate Coronavirus Disease 2019". *Journal of Clinical Investigation* 27 (2020).

14. Gao Y., *et al.* "Diagnostic utility of clinical laboratory data determinations for patients with the severe COVID-19". *Journal of Medical Virology* 17 (2020).

15. Yang X., *et al.* "Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study". *The Lancet Respiratory Medicine* 8.5 (2020):475-481.

16. Shen L., *et al.* "Clinical and laboratory-derived parameters of 119 hospitalized patients with coronavirus disease 2019 in Xiangyang, Hubei Province, China". *Journal of Infection* (2020).

17. Perico L., *et al.* "Should COVID-19 concern nephrologists? Why and to what extent? The emerging impasse of angiotensin blockade". *Nephron* 1.19 (2020).

18. Zhang L., *et al.* "Origin and evolution of the 2019 novel coronavirus". *Clinical Infectious Diseases* (2020).

19. Lippi G., *et al.* "Relation between red blood cell distribution width and inflammatory biomarkers in a large cohort of unselected out-patients". *Archives of Pathology and Laboratory Medicine* 133 (2009):628-632.

Volume 4 Issue 8 August 2020