Personalized therapy approach for hospitalized patients with COVID-19

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Abstract

Hospitalized patients with COVID-19 experiencing respiratory symptoms have different complications (inflammatory, co-infection and thrombotic) that are identifiable by analytics patterns. Personalized treatment decisions decreased early mortality (OR 0.144, CI 0.03–0.686; p=0.015). Increasing age (OR 1.06; p=0.038) and therapeutic effort limitation (OR 9.684; p<0.001) were associated with higher mortality.

Keywords: COVID-19, personalized therapy, pneumonia, patterns.

INTRODUCTION

The COVID-19 pandemic has witnessed doctors of different profiles have to shift responsibilities and become the primary physician for severe clinically similar patients with fever, dyspnea and respiratory deterioration. Respiratory symptoms are caused by different complications due to the cytopathic effect of the virus, dysregulated immune response, co-infections and/or pulmonary embolisms [1–3]. We hypothesized that patients have distinct analytics patterns that reflect various clinical complications and need different therapy approaches. In response, we designed an informatics tool that afforded us a real-time control center of patients, under the supervision of an expert infectious disease specialist.

We aimed to describe the main clinical complications of hospitalized patients with COVID-19 through classification into three pattern groups (inflammatory, co-infection and thrombotic), and demonstrate how personalized therapy for each pattern improves outcomes.

METHODS

Study Design, patients and data

Observational cohort study of all patients with COVID-19 (PCR and/or fulfilment of clinical diagnostic criteria) admitted to Hospital Clinic, Barcelona (March 28th - April 1st). All patients received lopinavir/ritonavir, hydroxychloroquine plus azithromycin. Our Institutional Ethics Committee approved the study.

Data concerning patients' characteristics, laboratory tests and microbiological results were retrieved from electronic health records with an informatics tool. Therapeutic effort limitation was defined as a life expectancy <6 months (considered no tributary of aggressive therapeutic measures). Three outcomes were considered at day 5 after identification: 1) improvement: FiO2 requirement reduction with respect to the inclusion day and improvement in O2 saturation; 2) torpid clinical course: increase, maintenance or reduction in oxygen rate by only one liter or lack of clinical improvement; 3) death.

Identification of different patterns and recommendations for personalized medicine

Based on analytics, three clinical patterns among COVID-19 hospitalizations were defined: 1) inflammatory, 2) co-infection and 3) thrombotic.

Inflammatory pattern comprised patients with a presumably excessive cytokine response caused by COVID-19. To define this pattern, we used CRP, ferritin, procalcitonin and creatinine. We excluded patients with plasma procalcitonin >2 ng/mL with creatinine <1.5 mg/dL, and those patients with other well-known clinical conditions that cause high levels of CRP or ferritin. Three clinical-inflammatory subset patterns were defined: a) CRP >10 mg/dL and ferritin <3000 ng/mL ("IL-6 profile"), b) CRP >10 mg/dL and ferritin >3000 ng/mL ("IL-6 and IL-1 profile"), and c) CRP <10 mg/dL

and ferritin >3000 ng/mL ("IL-1 profile"). We assumed these three patterns justified personalized therapy approaches: a) selective cytokine blockade of IL-6, b) cytokine blockade of IL-6 and IL-1, and c) selective cytokine blockade of IL-1.

Co-infection pattern comprised patients with plasma procalcitonin >2 ng/mL with creatinine <1.5 mg/dL. We considered a personalized therapy approach whenever infections were evaluated by appropriate microbiological cultures, and urinary antigen tests, and/or treated by modification/initiation of antibiotic therapy when necessary.

Thrombotic pattern comprised patients who were assumed to be coagulopathy events. This pattern was identified with CRP <10 mg/dL and ferritin <3000 ng/mL, and D-dimer and high-sensitivity troponin higher than 5000 ng/mL and 45.2 ng/L, respectively. We considered those patients followed a personalized therapy approach whenever pulmonary embolism was ruled out by CT scan and/or anticoagulation treatment was administered if CT scan was not performed.

Statistical analysis

Mann-Whitney U test, $\chi 2$ test and Fisher's exact test were used to compare differences between patients who did and did not receive a personalized therapy approach. A logistic regression model, including all variables related with mortality in univariate analyses ($p<0.05$)–age, hypertension, chronic heart disease, therapeutic effort limitation and personalized therapy approach–was performed to assess their independent association with mortality. Statistical analyses were performed with SPSS 22.0.

RESULTS

Of 786 patients, 246 were identified as belonging to one of the three patterns groups. Figure 1 described the length from illness onset to each clinical complication pattern. A total of 99 (40.2%) patients had underwent a personalized therapy approach according to our definitions, while 147 (59.8%) did not. Table 1 summarizes characteristics and outcomes of patients with different patterns.

Inflammatory pattern

Clinical inflammatory pattern occurred in 206 (83.4%) patients. Those in the high CRP and low ferritin group had received a prior immunomodulatory drug (2.3%) less frequently. Fifty-two (30.2%) patients received tocilizumab and 15 (8.7%) siltuximab, of whom 31 also received corticosteroids (24, methylprednisolone 250mg/day for 3 days, followed by 30 mg/day for 3 days; 1, dexamethasone 20mg/day for 5 days; 6, others). A specific IL-6 pathway inhibitor was not administered in the remaining 105 (61%) patients. Nineteen patients received methylprednisolone 250mg; 12, another dosage of methylprednisolone; 6, dexamethasone; and all others received no immunomodulatory treatment.

No prior immunomodulatory drugs were given to any patients belonging to the high ferritin and high CRP group. A total of 4 patients received tocilizumab (3) or siltuximab (1) plus anakinra with or without corticosteroids (3 and 1, respectively) and 7 of 11 did not receive this combination of inhibitors.

Most patients belonging to the high ferritin and low CRP group had received a prior immunomodulatory drug, primarily a specific IL-6 inhibitor (15 cases). Four of 23 patients received anakinra, and 19 of 23 did not receive a specific IL-1 pathway inhibitor.

Co-infection pattern

Of 16 (6.5%) patients with a co-infection pattern, 11 were evaluated for infection. Of these, 7 were diagnosed with a co-infection: ventilator-associated pneumonia (2 cases), invasive candidiasis (1), pneumococcal infection (1) and purulent tracheobronchitis with non-bacterial identification (3). Specific antibiotic treatment, commonly meropenem (64%), was administered. Infection was not ruled out in 5 patients.

Thrombotic pattern

Of 24 (9.7%) patients with a thrombotic pattern, anticoagulation treatment was administered in 13 cases. CT scan was performed on 7 of 13, as the remaining patients were severely ill and it was not possible. Pulmonary embolism was diagnosed in 6 of those cases. CT scans and anticoagulation treatments were not performed on 11 patients. Of these, 5 died. Causes of death were sudden death (3 cases), malignant arrhythmia (1) and multiorgan failure (1).

Outcomes

Improvement at day 5 occurred in 93.9% of patients included in the personalized therapy approach group and 59.9% ($p<0.001$) in the remaining. Torpid clinical course was documented in 25.3% and 61.2% ($p<0.001$), respectively, and early mortality at day 5 was 2% vs 17.7% ($p<0.001$). 14-day mortality was 20% vs 43.6% ($p=0.008$) and 28-day mortality was 20% vs 44.2% ($p=0.004$).

Multivariate analyses showed that personalized therapy was independently associated with decreased early mortality (OR 0.144; 95% confidence interval [CI], 0.03–0.686; $p=0.015$). Increasing age (OR 1.06; 95% CI, 1.003-1.121; $p=0.038$) and therapeutic effort limitation (OR 9.684; 95% CI,

2.934-31.959; p<0.001) were found as independent factors associated with higher mortality. The goodness of fit of the model was assessed by the Hosmer-Lemeshow test (p=0.275). The discriminatory power of the model had an AUC of 0.907 (95% CI, 0.847–0.967), demonstrating an excellent ability to predict mortality.

DISCUSSION

We identified analytics patterns that distinguished different clinical complications in patients with COVID-19. Inflammatory complications presenting in the most severe form as acute respiratory distress syndrome (ARDS) have been well described [4,5], acting as a main pathogenic role for IL-6 and IL-1 [6]. Some analytics markers are a reflex of cytokine patterns. CRP reflects the proinflammatory response mediated by IL-6 [7], while hyperferritinemia reveals immune dysregulation mainly mediated by IL-1 and INF-gamma [8,9]. We used analytics data to determine the need for IL-6 and IL-1 inhibitors, which have proven successful in prior studies [10,11].

Our results suggest that IL-6 is the first step of ARDS in patients with COVID-19. In concordance with other authors, flare-up of IL-6 occurred on day 10 [12]. After IL-6 blockade, ferritin continued to increase in all patients for 72 hours. After this period, a subgroup of patients with persistent elevation in ferritin levels (pattern 1c - mean time 13 days) was identified. This inflammatory pattern might correspond to an escape by other routes from the host's immune system.

Co-infection or pulmonary embolism are other important complications in patients with COVID-19 [3,12]. The most important demonstrable finding in our study has been that analytics-driven patterns reflect different clinical situations, which may result in a personalized therapy approach. Following recommendations derived from these patterns decreased mortality. Our objective is not

to supplant clinical judgment with respect to a specific patient; rather, we aim to offer an objective tool that may guide physicians in clinical decision-making processes.

Our unicenter study has some limitations. First, we have not reported a randomized controlled trial and there is potential for confounding effects. Future validation in a more extensive cohort is needed. Thirdly, we started the project with a comprehensive yet not scientifically-supported cut-off point for each analytics marker. Fourthly, most patients are included in the inflammatory pattern group. The small number of patients with other patterns poses a limitation. Finally, individuals who underwent a personalized therapy approach may have had better clinical conditions or were attended by more expert physicians.

In conclusion, we detailed that patients with COVID-19 have different complications identifiable by analytics patterns. Each situation requires a different therapy approach. Personalized therapy is an independent risk factor for survival.

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Table 1. Different pattern outcomes per treatment strategy.

INFLAMMATORY PATTERN			
	Personalized therapy approach N=75	**Non-personalized therapy approach N=133**	**p**
High R-CP and low ferritin pattern (HL)	**N=67**	**N=105**	
Age –Mean (SD), in years	60.7 (13.9)	68.3 (15.2)	0.001
Age-Median (IQR), in years	62 (53-72)	72 (58-80)	0.005
Gender male, N (%)	44 (65.7)	67(63.8)	0.803
Comorbidities			
Hypertension	32 (47.8)	59 (56.2)	.178
Diabetes mellitus	15 (22.4)	26 (24.8)	.434
Chronic heart disease	11 (16.4)	18 (17.1)	.538
Chronic lung disease	13 (19.4)	18 (17.1)	.428
Chronic liver disease	4 (6)	6 (5.7)	.595
Cancer	5 (7.5)	11 (10.5)	.353
Hematological diseases	2 (3)	4 (3.8)	.566
Others	48 (71.6)	78 (74.3)	.416
Therapeutic effort limitation	6 (9)	36 (34.3)	P<.001
Hospitalized			
In current ward	58 (86.6)	84 (80)	0.268
In ICU	9 (13.4)	21 (20)	
Outcome by day 5			
Improvement	65 (97)	66 (62.9)	P<0.001
Torpid clinical course	12 (17.9)	59 (56.2)	P<0.001
Death	0 (0)	15 (14.3)	0.001

High R-CP and high ferritin pattern (HH)	N=4	N=7	
Age –Mean (SD), in years	68.25 (4.5)	63.14 (16.3)	0.564
Age –Median (IQR), in years	68.5 (63-73.5)	73 (59-75)	0.545
Gender male, N (%)	4 (100)	7 (100)	1
Comorbidities			
Hypertension	2 (50)	1 (14.3)	.491
Diabetes mellitus	0	0	-
Chronic heart disease	1 (25)	1 (14.3)	.618
Chronic lung disease	2 (50)	2 (28.6)	.470
Chronic liver disease	0	2 (28.6)	.382
Cancer	1 (25)	1 (14.3)	.618
Hematological diseases	1 (25)	1 (14.3)	.618
Others	4 (100)	3 (42.9)	.104
Therapeutic effort limitation	0	2 (28.6)	.382
Hospitalized			
In current ward	4 (100)	4 (57.1)	0.212
In ICU	0 (0)	3 (42.9)	
Outcome by day 5			
Improvement	4 (100)	4 (42.9)	0.106
Torpid clinical course	1 (25)	5 (71.4)	0.197
Death	0	1 (14.3)	0.636
Low R-CP and high ferritin pattern (LH)	4	19	
Age –Mean (SD), in years	56.5 (5.7)	63.1 (10.32)	0.234
Age- Median (IQR), in years	55 (52-78)	64 (54.5-72.25)	0.590
Gender male, N (%)	4 (100)	16 (84.2)	0.547

Comorbidities			
Hypertension	3 (75)	10 (52.6)	.404
Diabetes mellitus	1 (25)	1 (5.3)	.324
Chronic heart disease	0	3 (15.8)	.547
Chronic lung disease	0	4 (21.1)	.438
Chronic liver disease	1 (25)	3 (15.8)	.562
Cancer	0	2 (10.5)	.676
Hematological diseases	1 (25)	2 (10.5)	.453
Others	4 (100)	12 (63.2)	.206
Therapeutic effort limitation	0	0	-
Hospitalized			
In current ward	1 (25)	7 (36.8)	0.565
In ICU	3 (75)	12 (63.2)	
Outcome by day 5			
Improvement	4 (100)	13 (68.4)	0.269
Torpid clinical course	1 (25)	12 (63.2)	0.200
Death	0	1 (5.3)	0.826
CO-INFECTION PATTERN			
	Personalized therapy approach N=11	**Non-personalized therapy approach N=5**	**p**
Age – Mean (SD), In years	64 (19.4)	73 (11.1)	0.355
Age- Median (IQR), in years	66 (53-76)	73 (63.5-82.5)	0.282
Gender male, N (%)	8 (72)	2 (40)	0.242
Comorbidities			
Hypertension	7 (63.6)	4 (80)	.484

Diabetes mellitus	3 (27.3)	1 (20)	.635
Chronic heart disease	1 (9.1)	2 (40)	.214
Chronic lung disease	4 (36.4)	1 (20)	.484
Chronic liver disease	0	0	-
Cancer	0	2 (40)	.083
Hematological diseases	0	1 (20)	.313
Others	10 (90.9)	5 (100)	.688
Therapeutic effort limitation	2 (18.2)	4 (80)	.036
Hospitalized			
In current ward	4 (36.4)	5 (100)	0.034
In ICU	7 (63.6)	0 (0)	
Outcome by day 5			
Improvement	9 (81.8)	1 (20)	0.036
Torpid clinical course	6 (54.5)	4 (80)	0.346
Death	0 (0)	4 (80)	0.03
THROMBOTIC PATTERN			
	Personalized therapy approach N=13	**Non-personalized therapy approach N=11**	**p**
Age –Mean (SD), in years	68.6 (15.2)	70.6 (13.1)	0.734
Age- Median (IQR), in years	74 (57.25-79.75)	72 (72-76)	1
Gender male, N (%)	13 (100)	7 (63.6)	0.031
Comorbidities			
Hypertension	7 (53.8)	2 (18.2)	.084
Diabetes mellitus	1 (7.7)	5 (45.5)	.048
Chronic heart disease	4 (30.8)	3 (27.3)	.605
Chronic lung disease	3 (23.1)	1 (9.1)	.363

Chronic liver disease	3 (23.1)	3 (27.3)	.590
Cancer	1 (7.7)	0	.542
Hematological diseases	0	0	-
Others	12 (92.3)	8 (72.7)	.233
Therapeutic effort limitation	3 (23.1)	3 (27.3)	.590
Hospitalized			
In current ward	6 (46.2)	4 (36.4)	0.628
In ICU	7 (53.8)	7 (63.6)	
Outcome by day 5			
Improvement	11 (84.6)	5 (45.5)	0.055
Torpid clinical course	5 (38.5)	10 (90.9)	0.011
Death	2 (15.4)	5 (45.5)	0.122

R-CP: Reactive- C Protein. ICU: Intensive Care Unit

Figure 1. Length from illness onset to each clinical complication pattern.

Figure 1