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Predicting Mortality Risk in Older Hospitalized Persons With COVID-19: A Comparison of the COVID-19 Mortality Risk Score with Frailty and Disability

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A B S T R A C T

Objectives: To assess the association of pre-morbid functional status [Barthel Index (BI)] and frailty [modified Frailty Index (mFI)] with in-hospital mortality and a risk scoring system developed for COVID-19 in patients ≥75 years diagnosed with COVID-19.
Design: Retrospective bicentric observational study.
Setting and Participants: Data on consecutive patients aged ≥75 years admitted with COVID-19 at 2 Italian tertiary care centers were collected from February 22 to May 30, 2020.
Methods: Overall, 221 consecutive patients with COVID-19 aged ≥75 years were admitted to 2 hospitals in the study period and were included in the analysis. Clinical, functional (BI), frailty (mFI), laboratory, and imaging data were collected. Mortality risk on admission was assessed with the COVID-19 Mortality Risk Score (COVID-19 MRS), a dedicated score developed for hospital triage.
Results: Ninety-seven (43.9%) patients died. BI, frailty, age, dementia, respiratory rate, Pa_{O_2}/Fi_{O_2} ratio, creatinine, and platelet count were associated with mortality. Analysis of the area under the receiver operating characteristic (AUC) indicated that the predictivity of age was modest and the combination of BI, mFI, and COVID-19 MRS yielded the highest prediction accuracy ($AUC_{COVID\text{-}19MRS+BI+mFI}$ vs AUC_{Age}: 0.87 vs 0.59; difference: +0.28, lower bound–upper bound: 0.17-0.34, $P < .001$).
Conclusions and Implications: Premorbid BI and mFI are associated with mortality and improved the accuracy of the COVID-19 MRS. Functional status may prove useful to guide clinical management of older individuals.

The first human cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were first reported in Wuhan, Hubei Province, China, in January 2020, then spreading worldwide and officially being declared a pandemic by the WHO on March 11, 2020.[1]

Since then, age was identified as the strongest risk factor for poor short-term outcome in patients diagnosed with SARS-CoV-2 disease (COVID-19).[2–4] Despite this, studies specifically targeting older patients (≥75 years) are few and, though at the highest risk of mortality, information on factors associated with adverse outcome in this

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population is limited.[5,6] Italy was the first country outside Asia to be heavily plagued by the virus, with more than 1 million confirmed cases since January 31, 2020,[7] with many older individuals involved.

Aim of this study was to assess the association of functional profile on mortality in patients ≥75 years admitted for COVID-19 to 2 tertiary care centers located in Lumbardy and Tuscany, and to analyze whether it may help stratify prognosis according to the COVID-19 Mortality Risk Score (COVID-19 MRS), a scoring system developed for rapid triage evaluation.[2]

Methods

Study Design

This is a retrospective observational study. The clinical history, laboratory, and imaging variables of patients consecutively admitted with proven COVID-19[8] to 2 Italian tertiary hospitals located respectively in Northern and Central Italy from February 22 to May 30, 2020, were collected on admission and reviewed. Only patients aged ≥75 years were included in the present analysis. Overall, 616 patients with COVID-19 were admitted to the 2 hospitals over the selected period, and the 221 aged ≥75 years constituted our study population.

Patient Characteristics

Hospital characteristics and organization during the pandemic wave, as well as methods used to collect clinical, laboratory, and imaging variables for each patient into a unique database, have been previously described.[2] Variables assessed on hospital admission for each patient were collected from electronic charts and included demographics, number of drugs prescribed prior to admission, cardiovascular risk factors (smoking history, hypertension, diabetes), and data on comorbidities (including information on active and nonactive cancer and cardiovascular and pulmonary diseases).

Functional status 2 weeks prior to hospitalization was routinely assessed with the Barthel Index by interviewing the patient and relatives by phone calls, in which lower values correspond to poorer functional status[9] and to poorer prognosis in the general older population.[10] Briefly, the Barthel Index summarizes functional independence in feeding, bathing, grooming, dressing, bowels, bladder, toilet use, transfers, mobility, and stairs. Frailty was assessed based on the modified Frailty Index (mFI) created by Saxton and Velanovich by mapping 11 variables (nonindependent functional status, history of diabetes mellitus, chronic obstructive pulmonary disease or pneumonia, heart failure, myocardial infarction, angina or coronary revascularization, hypertension, peripheral vascular disease, presence of impaired sensorium, TIA or cerebrovascular event without or with deficit) present in the Canadian Study of Health and Aging Frailty Index.[11] Frailty was defined by a score, equal to the ratio between present on total conditions, >0.36.[11] Information on respiratory support and drugs prescribed during hospital stay were collected as well. Six medical doctors collected the data into a unique database and independently reviewed their consistency. Data were last updated on May 30, 2020.

In accordance with Ethics Committees' indications at both hospitals, which approved data collection and granted a waiver of informed consent from study participants, patients' identity was anonymized, and information protected by password.

Clinical Severity on Admission

Baseline clinical severity was assessed with the COVID-19 Mortality Risk Score (COVID-19 MRS), a rapid, operator-independent clinical tool developed to stratify mortality risk at triage.[2] The 6 items of the score are age, number of comorbidities, respiratory rate, Pao_2/Fio_2, serum creatinine, and platelet count; each item is scored from 1 to 3 according to tertiles of phenotype severity. As previously described, mortality risk is classified as low (≤10), intermediate (11-13), and high (≥14).[2]

Study Outcomes

Predictive accuracy of the COVID-19 MRS and the association of disability (defined as a Barthel Index <75) and frailty with in-hospital mortality and their impact on the COVID-19 MRS risk stratification capability were the primary outcomes.

Statistical Analysis

Continuous variables, reported as mean ± standard deviation or as median with interquartile range, respectively for normal and non-normal distributions, were compared between groups ("survivor" vs "nonsurvivor" status) with *t* test or nonparametric tests, as appropriate. Categorical variables, reported as counts and percentages, were compared between groups with χ^2 test, or Fisher exact test when the expected cell count was less than 5.

Cox multivariable regression analysis (with backward stepwise deletion) was used to assess determinants of mortality. All variables with $P < .10$ were entered into the multivariable models, and a 2-sided $P < .05$ was considered statistically significant. Receiver operating characteristic analysis was used to compare prediction performance of the COVID-19 MRS with and without disability (as expressed by the Barthel Index) and frailty. Statistical analysis was performed using the SPSS, version 27.0, statistical package for Macintosh (IBM, Armonk, NY).

Results

Baseline Clinical Characteristics

As of May 30, a total of 124 (56.1%) of 221 patients [overall median age 82 (78-86) years, 60.6% men] had been discharged from hospital alive, whereas 97 (43.9%) had died.

The demographic and clinical characteristics of nonsurvivors and survivors are reported in Table 1. Nonsurvivors were significantly older, with no differences between men and women. Cardiovascular risk factors and comorbidities were similarly distributed in the 2 study groups. Nonsurvivors presented a higher degree of functional impairment (lower Barthel Index), frailty (as mFI), and dementia. Previous use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers was similar in both groups. At triage, nonsurvivors presented a higher COVID-19 MRS and more frequently reported preadmission insomnia. Other symptoms before admission were similarly prevalent in the 2 groups.

Laboratory and Imaging Findings

Laboratory findings are presented in Supplementary Table 1. In the population as a whole, the median Pao_2/Fio_2 ratio was 260 (interquartile range 204-406), and values < 200 were associated with a higher mortality. Lymphocytopenia was present in 69% of the population. Nonsurvivors had a lower platelet count, higher levels of serum creatinine, lactate dehydrogenase, and C-reactive protein. Furthermore, nonsurvivors presented with worse baseline inflammatory response. Chest radiograph was abnormal in 92.5% of cases.

Medical Management and Clinical Outcomes

Overall, 79.6% of patients received liberal oxygen and only 11.8% and 5.5% received, respectively, noninvasive and invasive ventilation,

Table 1
Clinical Characteristics on Hospital Admission by Survival Status

	Overall (N = 221)	Nonsurvivors (n = 97)	Survivors (n = 124)	*P*
Demographic Characteristics				
Age, median (IQR)	82 (78-86)	83 (79-87)	80 (77-85)	.011
Age >90 y	23 (10.4)	11 (11.3)	12 (9.7)	.69
Sex, male	134 (60.6)	62 (63.9)	72 (58.1)	.38
Smoking history	56 (25.3)	18 (18.6)	38 (30.6)	.043
Hypertension	113 (51.2)	51 (52.6)	62 (50.0)	.61
Diabetes mellitus	78 (35.3)	41 (42.3)	37 (29.2)	.06
CV disease	107 (48.4)	50 (51.5)	57 (46.0)	.41
Previous stroke/TIA	17 (7.7)	11 (11.3)	6 (4.8)	.07
COPD	36 (16.3)	13 (13.4)	23 (18.5)	.30
Cancer	34 (15.4)	19 (19.5)	15 (12.0)	.25
Depression	37 (16.7)	19 (19.5)	18 (14.5)	.59
Dementia	42 (19.0)	32 (33.0)	10 (8.1)	<.001
Comorbidities*, n, median (IQR)	3 (2-5)	4 (2-6)	3 (2-5)	.65
Frail	79 (35.7)	43 (44.3)	36 (29.0)	.019
Barthel Index, mean ± SD	80 ± 23	72 ± 27	82 ± 18	.009
<75	102 (46.2)	69 (71.1)	33 (26.6)	<.001
≥75	119 (53.8)	28 (28.9)	91 (73.4)	
Drugs, median (IQR)	5 (3-8)	5 (3-9)	4 (2-7)	.010
ACE-i/ARBs	84 (38.2)	32 (33.0)	52 (41.9)	.20
COVID-19 MRS				<.001
Low (≤10)	16 (7.2)	2 (2.1)	14 (11.3)	
Intermediate (11-13)	90 (40.7)	22 (22.7)	68 (54.8)	
High (≥14)	115 (52.1)	73 (75.3)	42 (33.9)	
Signs and symptoms				
Fever	179 (80.9)	82 (84.5)	97 (78.2)	.13
Cough	99 (44.7)	45 (46.3)	54 (43.5)	.66
Dyspnea	103 (46.6)	50 (51.5)	53 (42.7)	.16
Respiratory rate, median (IQR)	22 (20-28)	28 (21-33)	20 (18-24)	<.001
Insomnia	37 (16.7)	21 (21.6)	16 (12.9)	.043
Diarrhea	22 (10.0)	9 (9.3)	13 (10.5)	.79
Syncope	18 (8.1)	10 (10.3)	8 (6.5)	.298
Altered mental status	24 (10.9)	11 (11.3)	13 (10.5)	.80

ACE-i, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; COPD, chronic obstructive pulmonary disease; CV, cardiovascular disease; IQR, interquartile range; SD, standard deviation; TIA, transient ischemic attack.
Unless otherwise noted, values are n (%).
*Comorbidities is a composite variable including from hypertension to dementia.

more frequently nonsurvivors (Supplementary Table 1). Although antibiotics had been prescribed more frequently to nonsurvivors, prescription of heparin, hydroxychloroquine, and antiviral agents (combination of lopinavir/ritonavir) were all more frequently prescribed to survivors. Notably, there was no association of Barthel Index with treatment strategies (Supplementary Table 2).

Determinants of Mortality and Outcome Prediction by the COVID-19 MRS

Cox multivariable regression analysis (Table 2, Model 1) indicated that absence of disability (higher Barthel index), P_{aO_2}/Fio_2 ratio, and platelet count were positively associated, whereas age, presence of dementia, and higher respiratory rates and serum creatinine levels were negatively associated with survival. Similarly, a higher Barthel Index and lack of frailty were associated with a better outcome after adjusting for COVID-19 MRS risk category (Table 2, Model 2).

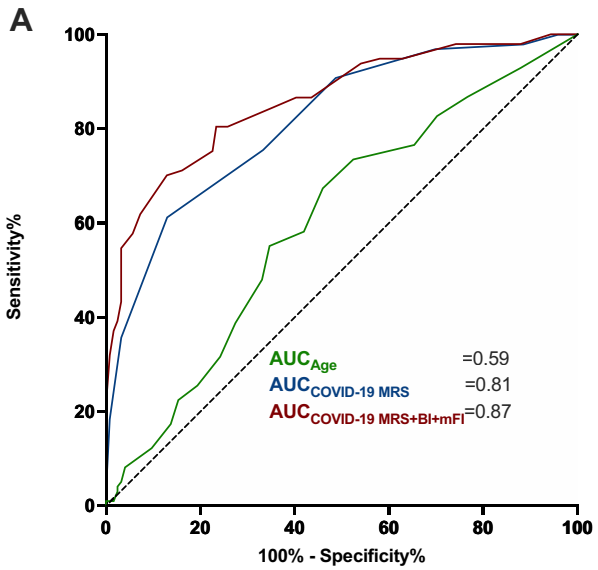
Analysis of the area under the receiver operating characteristic (AUC) indicated that the predictive power for mortality of age alone was modest.

Comparison of AUCs (Figure 1A) revealed that the overall prediction quality increased by using the COVID-19 MRS score ($AUC_{COVID\text{-}19\ MRS}$ vs AUC_{Age}: 0.81 vs 0.59; difference: +0.21, lower bound–upper bound 0.12-0.34; $P < .001$) and the score combined with the BI and mFI ($AUC_{COVID\text{-}19\ MRS+BI+mFI}$ vs $AUC_{COVID\text{-}19\ MRS}$: 0.87 vs 0.81; difference: +0.06, lower bound–upper bound: 0.02-0.08, $P = .005$;

Table 2
Cox Multivariable Regression Analysis of Determinants of In-Hospital Mortality

Model 1: Clinical and Laboratory Variables				Model 2			
Variables	HR	95% CI	*P*	Variables	HR	95% CI	*P*
Barthel Index, (≥75 vs < 75)	0.383	0.24-0.62	<.001	COVID-19 MRS, (for unitary increase)	1.49	1.33-1.69	<.001
Age (per year increase)	1.06	1.01-1.11	.015				
Dementia (no vs yes)	0.52	0.31-0.88	.015	Barthel Index (≥75 vs < 75)	0.35	0.22-0.57	<.001
RR (per breaths/min increase)	1.06	1.02-1.09	<.001	Frailty (no vs yes)	0.60	0.39-0.94	.024
Pao_2/Fio_2 (per unit increase)	0.995	0.994-0.999	.019				
Creatinine (per mg/dL increase)	1.20	1.04-1.39	.012				
Platelets (10^9/L per unit increase)	0.997	0.992-0.998	.003				

CI, confidence interval; HR, hazard ratio; RR, respiratory rate.
Variables excluded ($P > .10$) from Model 1: frailty, number of drugs, C-reactive protein, and number of comorbidities.



B

COVID-19 MRS	Sensitivity	1-Specificity
7	100	100
8	100	98
9	100	96
10	98	89
11	97	70
12	91	49
13	75	34
14	61	14
15	35	4
16	19	1
17	3	0
18	0	0

Fig. 1. ROC analysis. (A) Comparison of COVID-19 Mortality Risk Score (COVID-19 MRS) ROC curves with and without Barthel Index (BI) and modified Frailty Index (mFI) and Age. (B) Coordinates of the ROC curve for the COVID-19 MRS (all values for sensitivity and 1 − specificity are percentages). ROC, receiver operating characteristic.

$AUC_{COVID\text{-}19\ MRS+BI+mFI}$ vs AUC_{Age}: 0.87 vs 0.59; difference: +0.28, lower bound–upper bound: 0.17-0.34, $P < .001$). The final model combining the Barthel Index and the mFI explained 49% (Nagelkerke R^2) of the variance in COVID-19 related mortality and correctly classified 80% of cases (overall sensitivity: 70%; specificity 87%). Notably, the greatest improvement in the predictive accuracy of COVID-19 MRS was obtained for scores ≥14 (Figure 1B).

Discussion

In this study, almost 50% of patients aged >75 years admitted for COVID-19 died during hospitalization. Case fatality rates have been reported variably and are approximately 0.1% in children, but as high as 15% in old Chinese patients and even higher in older Italians or US citizens.[12–14] Viral shedding, atypical symptoms, lower cardiorespiratory reserve, and a proinflammatory status have been all postulated as potential causes of such an age-associated poor prognosis.[15,16]

In our study, worse functional profile (moderate to severe disability as expressed by the Barthel Index), age, dementia, respiratory rate, platelet count, serum creatinine, and Pa_{O_2}/Fi_{O_2} ratio, but not the number of comorbidities, were associated with in-hospital mortality. Furthermore, although age had a modest predictive role, with an AUC of 0.59, frailty (as expressed as the mFI) and functional profile were closely associated to the outcome and added to the predictive power of the COVID-19 MRS, with a final AUC of 0.87. This confirms the relevance of overall physical functioning, above and beyond disease severity and level of comorbidity, in determining the risk of death in older populations.[6,17,18] This message has direct clinical implications when choosing therapeutic strategies at hospital admission: older patients should be routinely assessed for frailty and disability in order to identify appropriate therapeutic strategies. The burden of COVID-19 pandemic in Italy was unique and overwhelming, posing the healthcare system into strain and presenting with difficult challenges. Overall, our results underscore the importance of an integrated assessment to avoid misplaced health priorities and ageism.[19]

Compared with other series of patients with COVID-19 that included younger individuals, our patients presented with an average greater burden of chronic comorbidities and, accordingly, of prescribed drugs.[20–22] Advanced age per se and associated chronic comorbidities have been identified as the strongest predictors of mortality in patients diagnosed with COVID-19.[4] In our patients older than 75 years, functional profile 2 weeks prior to hospitalization and the mFI predicted in-hospital mortality and increased the predictive power of the COVID-19 MRS, confirming the importance of comprehensive geriatric assessment as part of the admission evaluation.

As a case in point, in older patients hospitalized for pneumonia, functional status and frailty were independently associated with short- and long-term mortality.[23] Frailty, although difficult to define and quantify objectively, is generally intended as an impairment in muscular function associated with reduced homeostatic capacity in front of acute stressors[24] and is reported as an accurate predictor of adverse health outcomes, both in acute care settings[25] and in elective procedures.[26]

More recently, a report from the COPE cohort study showed that in individuals with COVID-19, length of hospital stay and mortality were associated with frailty.[27] Our results extend this concept by showing that the definition of the functional profile prior to COVID-19 may refine the assessment of prognosis defined by a disease-specific prognostic score such as the COVID-19 MRS.

Limitations

Some limitations of our study have to be acknowledged. First, the observational nature of our analysis does not allow to draw any firm conclusion about clinical determinants of mortality and associations with therapeutic strategies that, moreover, were clearly adapted over time. In addition, some laboratory parameters, which proved to be of prognostic relevance in other studies,[28,29] were not collected for all individuals in our sample, possibly as a consequence of variable severity of some clinical pictures (ie, very mildly affected vs extremely critical patients at presentation). Last, there are 2 main operational definitions of frailty, the physical phenotype and the multidomain phenotype. The physical phenotype—described by Fried et al[30] as the presence of unintentional weight loss, exhaustion, weakness, slow walking speed, and low level of physical activity—was difficult to derive in our acute hospital patients. For this reason, we assessed frailty using the mFI.[11]

Conclusions and Implications

Almost 1 in 2 patients ≥75 years diagnosed with COVID-19 died during hospitalization. Functional profile at 2 weeks before disease and assessment of frailty seem to be important factors in determining the in-hospital prognosis irrespective of age and comorbidities and help to increase accuracy of the COVID-19 MRS. Older patients diagnosed with COVID-19 should be reassessed in light of their personal history, fitness, frailty, and disability so that more focused and dedicated care can be provided.

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Supplementary Table 1
Laboratory, Imaging Findings on Admission and Treatment Strategies by Survival Status

	Overall (N = 221)	Nonsurvivors (n = 97)	Survivors (n = 124)	*P*
Laboratory findings				
Pao_2/Fio_2	260 (204-406)	230 (161-265)	288 (250-331)	<.001
Pao_2/Fio_2 <200, n (%)	54 (24.4)	36 (37.1)	18 (14.5)	<.001
Hematocrit, %	40 (36-44)	39 (35-43)	41 (37-44)	.039
Hemoglobin, g/dL	12.8 (11.4-13.9)	12.8 (11.2-13.9)	12.9 (11.5-13.9)	.64
WBC, $\times 10^9$/L	7.00 (5.00-9.54)	7.79 (5.2-10.60)	6.83 (4.93-8.42)	.022
Lymphocytes, $\times 10^9$/L	0.82 (0.56-1.12)	0.77 (0.51-1.08)	0.84 (0.63-1.19)	.013
Lymphocytopenia, n (%)	151 (68.9)	70 (72.2)	81 (66.4)	.36
Platelets, $\times 10^9$/L	187 (138-236)	159 (118-221)	201 (160-247)	<.001
ALT, U/L	22 (15-34)	25 (16-39)	20 (14-32)	.15
AST, U/L	38 (25-60)	45 (34-72)	31 (22-48)	.09
Serum creatinine, mg/dL	1.10 (0.81-1.54)	1.23 (0.92-1.84)	0.98 (0.77-1.33)	<.001
CPK, U/L	103 (57-158)	130 (78-262)	86 (47-160)	.09
LDH, U/L	347 (247-500)	489 (344-530)	277 (222-371)	<.001
CRP, mg/L	93 (47-159)	134 (66-188)	68 (36-137)	<.001
Variables not available in all patients				
Albumin (n = 130), g/L	3.1 (2.9-3.3)	3.0 (2.8-3.2)	3.2 (3.0-3.3)	<.001
BUN (n = 138), mg/dL	54 (38-74)	62 (45-89)	42 (32-63)	<.001
Ferritin (n = 118), ng/mL	523 (232-995)	692 (470-2203)	444 (218-823)	.005
D-Dimer (n = 116), ug/L	1250 (744-3426)	1678 (951-8872)	1105 (648-1881)	<.001
Procalcitonin (n = 118), ng/mL	0.16 (0.10-0.50)	0.34 (0.16-3.38)	0.13 (0.07-0.36)	.001
IL-6 (n = 105), pg/mL	23.0 (9.6-64.3)	56.2 (22.0-135.8)	18.9 (7.9-50.6)	<.001
TNF-α (n = 50), pg/mL	8.5 (4.9-15.1)	8.8 (4.7-14.5)	8.2 (4.9-15.1)	.64
Imaging: Chest radiograph, n (%)	(n = 213)	(n = 91)	(n = 122)	
Negative	18 (8.5)	5 (5.5)	13 (10.7)	.26
Consolidation	40 (18.8)	14 (15.4)	26 (21.3)	
Interstitial	123 (57.7)	59 (64.8)	64 (52.5)	
Mixed	32 (15)	13 (14.3)	19 (15.6)	
Treatment strategies, n (%)				
Respiratory support				
None	7 (3.2)	1 (1.0)	6 (4.8)	.006
Oxygen	176 (79.6)	71 (73.2)	105 (84.7)	
Noninvasive ventilation	26 (11.8)	19 (19.6)	7 (5.6)	
Invasive ventilation	12 (5.5)	6 (6.2)	6 (4.8)	
Drugs				
Antibiotics	181 (81.9)	87 (89.7)	94 (75.8)	.008
Heparin	143 (64.7)	49 (50.5)	94 (75.8)	<.001
Hydroxychloroquine	110 (49.8)	37 (39.1)	73 (58.9)	.002
Lopinavir or ritonavir	107 (48.4)	34 (35.1)	73 (58.9)	.001
Corticosteroids	71 (32.1)	39 (40.2)	32 (25.8)	.023

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CPK, creatine phosphokinase; CRP, C-reactive protein; IL-6, interleukin-6; LDH, lactate dehydrogenase; TNF-α, tumor necrosis factor alpha; WBC, white blood cell.
Unless otherwise noted, values are median (interquartile range).

Supplementary Table 2
Treatment Strategies by Barthel Index

Treatment Strategies	Barthel Index		*P*
	<75 (n = 102)	≥75 (n = 119)	
Respiratory support			
None	2 (2.0)	5 (4.2)	.63
Oxygen	82 (80.4)	94 (79.0)	
Noninvasive ventilation	11 (10.8)	15 (12.6)	
Invasive ventilation	7 (3.2)	5 (2.3)	
Drugs			
Antibiotics	79 (77.5)	102 (85.7)	.11
Heparin	64 (62.7)	79 (66.4)	.57
Hydroxychloroquine	58 (56.9)	52 (43.7)	.05
Lopinavir or ritonavir	56 (54.9)	51 (42.9)	.07
Corticosteroids	40 (39.2)	31 (26.1)	.037