CORRESPONDENCE

COVID-19 CASES

To rapidly communicate information on the global clinical effort against Covid-19, the Journal *has initiated a series of case reports that offer important teaching points or novel findings. The case reports should be viewed as observations rather than as recommendations for evaluation or treatment. In the interest of timeliness, these reports are evaluated by in-house editors, with peer review reserved for key points as needed.*

Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young

We report five cases of large-vessel stroke in patients younger than 50 years of age who presented to our health system in New York City. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was diagnosed in all five patients.

Cough, headache, and chills lasting 1 week developed in a previously healthy 33-year-old woman (Patient 1) (Table 1). She then had progressive dysarthria with both numbness and weakness in the left arm and left leg over a period of 28 hours. She delayed seeking emergency care because of fear of Covid-19. When she presented to the hospital, the score on the National Institutes of Health Stroke Scale (NIHSS) was 19 (scores range from 0 to 42, with higher numbers indicating greater stroke severity), and computed tomography (CT) and CT angiography showed a partial infarction of the right middle cerebral artery with a partially occlusive thrombus in the right carotid artery at the cervical bifurcation. Patchy ground-glass opacities in bilateral lung apices were seen on CT angiography, and testing to detect SARS-CoV-2 was positive. Antiplatelet therapy was initiated; it was subsequently switched to anticoagulation therapy. Stroke workup with echocardiography and magnetic resonance imaging of the head and neck did not reveal the source of the thrombus. Repeat CT angiography on hospital day 10 showed complete resolution of the thrombus, and the patient was discharged to a rehabilitation facility.

Over a 2-week period from March 23 to April 7, 2020, a total of five patients (including the aforementioned patient) who were younger than 50 years of age presented with new-onset symptoms of large-vessel ischemic stroke. All five patients tested positive for Covid-19. By comparison, every 2 weeks over the previous 12 months, our service has treated, on average, 0.73 patients younger than 50 years of age with large-vessel stroke.

On admission of the five patients, the mean NIHSS score was 17, consistent with severe large-vessel stroke. One patient had a history of stroke. Other pertinent clinical characteristics are summarized in Table 1.

A retrospective study of data from the Covid-19 outbreak in Wuhan, China, showed that the incidence of stroke among hospitalized patients with Covid-19 was approximately 5%; the youngest patient in that series was 55 years of age.[1] Moreover, large-vessel stroke was reported in association with the 2004 SARS-CoV-1 outbreak in Singapore.[2] Coagulopathy and vascular endothelial dysfunction have been proposed as complications of Covid-19.[3] The association between large-vessel stroke and Covid-19 in young patients requires further investigation.

Social distancing, isolation, and reluctance to present to the hospital may contribute to poor outcomes. Two patients in our series delayed calling an ambulance because they were concerned about going to a hospital during the pandemic.

Table 1. Clinical Characteristics of Five Young Patients Presenting with Large-Vessel Stroke.*

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age — yr	33	37	39	44	49
Sex	Female	Male	Male	Male	Male
Medical history and risk factors for stroke†	None	None	Hyperlipidemia, hypertension	Undiagnosed diabetes	Mild stroke, diabetes
Medications	None	None	None	None	Aspirin (81 mg), atorvastatin (80 mg)
NIHSS score‡					
On admission	19	13	16	23	13
At 24 hr	17	11	4	19	11
At last follow-up	13 (on day 14)	5 (on day 10)	NA; intubated and sedated, with multiorgan failure	19 (on day 12)	7 (on day 4)
Outcome status	Discharged to rehabilitation facility	Discharged home	Intensive care unit	Stroke unit	Discharged to rehabilitation facility
Time to presentation — hr	28	16	8	2	8
Signs and symptoms of stroke	Hemiplegia on left side, facial droop, gaze preference, homonymous hemianopia, dysarthria, sensory deficit	Reduced level of consciousness, dysphasia, hemiplegia on right side, dysarthria, sensory deficit	Reduced level of consciousness, gaze preference to the right, left homonymous hemianopia, hemiplegia on left side, ataxia	Reduced level of consciousness, global dysphasia, hemiplegia on right side, gaze preference	Reduced level of consciousness, hemiplegia on left side, dysarthria, facial weakness
Vascular territory	Right internal carotid artery	Left middle cerebral artery	Right posterior cerebral artery	Left middle cerebral artery	Right middle cerebral artery
Imaging for diagnosis	CT, CTA, CTP, MRI	CT, CTA, MRI	CT, CTA, CTP, MRI	CT, CTA, MRI	CT, CTA, CTP
Treatment for stroke	Apixaban (5 mg twice daily)	Clot retrieval, apixaban (5 mg twice daily)	Clot retrieval, aspirin (81 mg daily)	Intravenous t-PA, clot retrieval, hemicraniectomy, aspirin (81 mg daily)	Clot retrieval, stent, aspirin (325 mg daily), clopidogrel (75 mg daily)
Covid-19 symptoms	Cough, headache, chills	No symptoms; recently exposed to family member with PCR-positive Covid-19	None	Lethargy	Fever, cough, lethargy
White-cell count — per mm^3	7800	9900	5500	9000	4900

Platelet count — per mm³	427,000	299,000	135,000	372,000	255,000	
Prothrombin time — sec	13.3	13.4	14.4	12.8	15.2	
Activated partial-thromboplastin time — sec	25.0	42.7	27.7	26.9	37.0	
Fibrinogen — mg/dl	501	370	739	443	531	
D-dimer — ng/ml	460	52	2230	13,800	1750	
Ferritin — ng/ml	7	136	1564	987	596	

* Reference ranges are as follows: platelet count, 150,000 to 450,000 per cubic millimeter; prothrombin time, 12.3 to 14.9 seconds; activated partial-thromboplastin time, 25.4 to 34.9 seconds; fibrinogen, 175 to 450 mg per deciliter; D-dimer, 0 to 500 ng per milliliter; and ferritin, 30 to 400 ng per milliliter. CT denotes computed tomography, CTA CT angiography, CTP CT perfusion, MRI magnetic resonance imaging, NA not applicable, PCR polymerase chain reaction, and t-PA tissue plasminogen activator.
† The patients were screened for smoking, hypertension, hyperlipidemia, diabetes, atrial fibrillation, congestive heart failure, illicit drug use, and neck trauma.
‡ Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher numbers indicating more severe stroke.

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Disclosure forms provided by the authors are available with the full text of this case at NEJM.org.

We dedicate this case to our inspiring colleague Gary Sclar, M.D., a neurologist who died of Covid-19.

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Risk Factors for Mortality in Patients with COVID-19 in New York City

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BACKGROUND: New York City emerged as an epicenter of the coronavirus disease 2019 (COVID-19) pandemic.
OBJECTIVE: To describe the clinical characteristics and risk factors associated with mortality in a large patient population in the USA.
DESIGN: Retrospective cohort study.
PARTICIPANTS: 6493 patients who had laboratory-confirmed COVID-19 with clinical outcomes between March 13 and April 17, 2020, who were seen in one of the 8 hospitals and/or over 400 ambulatory practices in the New York City metropolitan area
MAIN MEASURES: Clinical characteristics and risk factors associated with in-hospital mortality.
KEY RESULTS: A total of 858 of 6493 (13.2%) patients in our total cohort died: 52/2785 (1.9%) ambulatory patients and 806/3708 (21.7%) hospitalized patients. Cox proportional hazard regression modeling showed an increased risk of in-hospital mortality associated with age older than 50 years (hazard ratio [HR] 2.34, CI 1.47–3.71), systolic blood pressure less than 90 mmHg (HR 1.38, CI 1.06–1.80), a respiratory rate greater than 24 per min (HR 1.43, CI 1.13–1.83), peripheral oxygen saturation less than 92% (HR 2.12, CI 1.56–2.88), estimated glomerular filtration rate less than 60 mL/min/1.73m^2 (HR 1.80, CI 1.60–2.02), IL-6 greater than 100 pg/mL (HR 1.50, CI 1.12–2.03), D-dimer greater than 2 mcg/mL (HR 1.19, CI 1.02–1.39), and troponin greater than 0.03 ng/mL (HR 1.40, CI 1.23–1.62). Decreased risk of in-hospital mortality was associated with female sex (HR 0.84, CI 0.77–0.90), African American race (HR 0.78 CI 0.65–0.95), and hydroxychloroquine use (HR 0.53, CI 0.41–0.67).
CONCLUSIONS: Among patients with COVID-19, older age, male sex, hypotension, tachypnea, hypoxia, impaired renal function, elevated D-dimer, and elevated troponin were associated with increased in-hospital mortality and hydroxychloroquine use was associated with decreased in-hospital mortality.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) is a pandemic that has impacted medical systems, societies, and economies worldwide. The first case of COVID-19, caused by severe acute respiratory syndrome 2 virus (SARS-CoV-2)[1], was reported in China in December 2019[2]. The virus has spread globally at a rapid pace, resulting in more than 2 million confirmed cases as of April 17, 2020[3]. In recent weeks, New York City has emerged as an epicenter of the pandemic, with over 120,000 confirmed cases and over 13,000 deaths due to confirmed or probable COVID-19 death as of April 17, 2020[4]. Studies of the clinical characteristics and epidemiologic characteristics of COVID-19 have been conducted in countries experiencing outbreaks earlier than the USA[5–11]. Large-scale observational data of the clinical characteristics and outcomes of COVID-19 in the population of the USA are scarce. In this study, we describe the clinical characteristics of COVID-19 in ambulatory and inpatient settings and identify risk factors associated with mortality in hospitalized patients.

METHODS

Study Design and Participants

A multicenter retrospective cohort study of patients with COVID-19 patients was conducted using the medical records of the Mount Sinai Health System, a large urban health system of 8 hospitals and more than four hundred ambulatory practices in the New York City metropolitan area. Patients with a positive SARS-CoV-2 test result and an encounter with a healthcare provider for COVID-19 between March 12 and April 17, 2020, were included in this study. A confirmed case of COVID-19 was defined as a positive result on reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay of nasopharyngeal swab specimens. The study population was dichotomized into ambulatory and hospitalized groups. The former included patients whose encounter was an office visit,

emergency department (ED) visit, or telehealth/telemedicine. Inpatients and ambulatory patients who were subsequently admitted to the hospital were included in the hospitalized group.

Both groups were further subdivided into survivors and non-survivors. Ambulatory non-survivors were patients who had expired prior to presentation to the ED, who had expired in the ED prior to admission to the hospital units, or who had an office or telemedicine encounter and were later found out to be deceased. Ambulatory survivors included all other ambulatory patients. Hospitalized non-survivors were patients who had expired as of April 17, 2020. Hospitalized survivors were patients who had been discharged home or to other facilities as of April 17, 2020.

Icahn School of Medicine at Mount Sinai has waived informed consent and Institutional Review Board approval because the study used a de-identified database.

Definitions

The following covariates were extracted from the database: patients' age, sex, ethnicity, race, smoking status, vital signs including temperature, peripheral oxygen saturation (SpO_2), heart rate, respiratory rate (RR), blood pressure (BP), body mass index (BMI), and laboratory results including white blood cell count (WBC), D-dimer, interleukin-6 (IL-6), hemoglobin, estimated glomerular filtration rate (eGFR), alanine aminotransferase (ALT), aspartate aminotransferase (AST), C-reactive protein (CRP), procalcitonin, ferritin, lactate dehydrogenase (LDH), fibrinogen (FBG), interleukin-6 (IL-6), comorbidities, and treatments.

Statistical Analysis

Continuous variables were reported as median with interquartile range. Categorical variables were expressed as proportions. Temporary changes of vital signs and laboratory values in survivors and non-survivors for the first 14 days after admission were assessed. To illustrate the risk associated with changes in the continuous variables, including vital signs and laboratory values, multivariate generalized additive models were used to calculate the odds ratio (OR) for mortality, with each median value set as a reference (i.e., OR = 1). The hazard ratio (HR) of each variable for mortality risk was assessed using univariate Cox proportional hazard regression model. To account for missing data values for laboratory results, we introduced multiple imputation, which is a procedure used to replace missing values with other plausible values by creating multiple filling-in patterns to avert bias caused by missing data. Using the dataset with imputed values, univariate and multivariate Cox model were fit to calculate HR.

The multivariate Cox model was adjusted for the following variables assessed in the univariate Cox model: patients' age, sex, race, cigarette use history, past medical history of asthma, hypertension, diabetes, or cancer, systolic BP, RR, SpO_2, BMI, initial laboratory values (lymphocyte proportion, D-dimer, IL-6), and hydroxychloroquine use. For this Cox regression analysis, we excluded variables from the univariable analysis if their between-group differences were not significant, if the number of events was too small to calculate hazard ratios, or if they had collinearity with other significant values. Each hospital was considered by the clustering term in the Cox proportional hazard model analysis where the clustering effect associated with hospitals was accounted for by the robust sandwich estimator. Preliminary confirmation of predictability of the Cox proportional hazard model demonstrated the area under the curve (AUC) to be 0.808 (95% CI, 0.790–0.825, Supplementary Figure 1). To investigate the effect of hydroxychloroquine while addressing the imbalance among treatment groups, we introduced inverse probability weighting (IPTW) based on propensity scoring to control for observed differences in baseline characteristics between treatment group and control group. IPTW was calculated based on the same variables as used in the Cox regression models, except for hydroxychloroquine use. We then fitted an IPTW-adjusted Cox with doubly robust methods. Survival curves with stratification for hydroxychloroquine were constructed using the Kaplan-Meier method. All statistical analyses were performed using version 3.6.2 of the R programming language (R Project for Statistical Computing; R Foundation).

RESULTS

Demographic and Clinical Characteristics

Between March 13 and April 17, there were 6493 confirmed COVID-19 cases, including 2785 (42.9 %) ambulatory patients and 3708 (57.1%) hospitalized patients. The demographics, clinical characteristics, and laboratory findings are shown in Table 1. The median age of the group was 59 (interquartile range [IQR] 43 to 72) with 66.6% of the patients older than 50 years of age. 45.5% of the patients were female. Based on patients' self-reported race, 26.9% were white, 24.1% were African American, 4.4% were Asian, and 44.7% were other. Based on self-reported ethnicity, 57.5% were Non-Hispanic, 25.4% were Hispanic, and the rest were unknown or not reported.

Ambulatory and Hospitalized Comparison

The median age was 47 years old in the ambulatory group (IQR 34 to 60) and 66 years old in the hospitalized group (IQR 55 to 78). 858 patients died (13.2%): 52 patients in the ambulatory group (1.9%) and 806 patients in the hospitalized group (21.7%). Among ambulatory patients, 69% were emergency room encounters without hospital admission, 18.2% were office-based encounters, and 1.4% were telemedicine encounters.

Compared with that of ambulatory patients, a higher proportion of hospitalized patients were older, were male, or had a history of cigarette use. Hospitalized patients were more likely

Table 1 Clinical Characteristics of the Patients with COVID-19

	Total (n = 6493)	Ambulatory (n = 2785)	Hospitalized (n = 3708)
Demographics			
Age (median [IQR])	59 [43, 72]	47 [34, 60]	66 [55, 78]
Age—no./total no. (%)			
< 50 years old	2169/6493 (33.4)	1531/2785 (55.0)	638/3708 (17.2)
50–74 years old	2996/6493 (46.1)	1081/2785 (38.8)	1915/3708 (51.6)
≥ 75 years old	1328/6493 (20.5)	173/2785 (6.2)	1155/3708 (31.1)
Female—no./total no. (%)	2955/6493 (45.5)	1362/2785 (48.9)	1593/3708 (43.0)
Race—no./total no. (%)			
White	1745/6493 (26.9)	817/2785 (29.3)	928/3708 (25.0)
African American	1564/6493 (24.1)	650/2785 (23.3)	914/3708 (24.6)
Asian	283/6493 (4.4)	127/2785 (4.6)	156/3708 (4.2)
Others	2901/6493 (44.7)	1191/2785 (42.8)	1710/3708 (46.1)
Ethnicity—no./total no. (%)			
Non-Hispanic	3734/6493 (57.5)	1543/2785 (55.4)	2191/3708 (59.1)
Hispanic	1652/6493 (25.4)	635/2785 (22.8)	1017/3708 (27.4)
Unknown	1107/6493 (17.0)	607/2785 (21.8)	500/3708 (13.5)
History of cigarette use—no./total no. (%)	1338/6493 (20.6)	429/2785 (15.4)	909/3708 (24.5)
Body mass index (kg/m^2) (median [IQR])	27.7 [24.3, 32.4]	27.4 [24.1, 31.9]	27.9 [24.3, 32.6]
Body mass index ≥ 30 kg/m^2—no./total no. (%)	1557/4399 (35.4)	359/1119 (32.1)	1198/3280 (36.5)
Encounter type—no./total no. (%)			
Hospital	5631/6493 (86.7)	1923/2785 (69.0)	3708/3708 (100.0)
Clinic/office	506/6493 (7.8)	506/2785 (18.2)	0/3708 (0.0)
Phone/telemedicine	318/6493 (4.9)	318/2785 (11.4)	0/3708 (0.0)
Others	38/6493 (0.6)	38/2785 (1.4)	0/3708 (0.0)
Past medical history—no./total no. (%)			
Asthma	271/6493 (4.2)	98/2785 (3.5)	173/3708 (4.7)
Chronic pulmonary obstructive disease	176/6493 (2.7)	26/2785 (0.9)	150/3708 (4.0)
Hypertension	1637/6493 (25.2)	365/2785 (13.1)	1272/3708 (34.3)
Obesity	418/6493 (6.4)	130/2785 (4.7)	288/3708 (7.8)
Diabetes	1151/6493 (17.7)	250/2785 (9.0)	901/3708 (24.3)
Chronic kidney disease	525/6493 (8.1)	94/2785 (3.4)	431/3708 (11.6)
Human immunodeficiency virus infection	98/6493 (1.5)	34/2785 (1.2)	64/3708 (1.7)
Cancer	413/6493 (6.4)	159/2785 (5.7)	254/3708 (6.9)
Vital signs—no./total no. (%)			
Temperature ≥ 39 °C	1215/6039 (20.1)	113/2332 (4.8)	1102/3707 (29.7)
Peripheral oxygen saturation (SpO_2)			
> 92%	4938/5702 (86.6)	2140/2201 (97.2)	2798/3501 (79.9)
88–92%	502/5702 (8.8)	39/2201 (1.8)	463/3501 (13.2)
≤ 87%	262/5702 (4.6)	22/2201 (1.0)	240/3501 (6.9)
Heart rate > 120 beats per min	539/5973 (9.0)	116/2265 (5.1)	423/3708 (11.4)
Respiratory rate			
≤ 24 per min	5155/5811 (88.7)	2050/2103 (97.5)	3105/3708 (83.7)
25–30 per min	390/5811 (6.7)	36/2103 (1.7)	354/3708 (9.5)
> 30 per min	266/5811 (4.6)	17/2103 (0.8)	249/3708 (6.7)
Systolic blood pressure < 90 mmHg	121/5834 (2.1)	26/2138 (1.2)	95/3696 (2.6)
Diastolic blood pressure < 60 mmHg	664/5834 (11.4)	155/2138 (7.2)	509/3696 (13.8)
Laboratory results			
WBC (× 10^3/μL) (median [IQR])	7.30 [5.40, 10.30]	6.20 [4.66, 8.36]	7.60 [5.50, 10.6]
< 4.0 × 10^3/μL—no./total no. (%)	380/4353 (8.7)	106/703 (15.1)	274/3650 (7.5)
4.0–8.0 × 10^3/μL—no./total no. (%)	3246/4353 (74.6)	538/703 (76.5)	2708/3650 (74.2)
> 12.0 × 10^3/μL—no./total no. (%)	727/4353 (16.7)	59/703 (8.4)	668/3650 (18.3)
Neutrophil			
Count (× 10^3/μL) (median [IQR])	5.60 [3.80, 8.20]	4.20 [2.90, 6.12]	5.80 [4.00, 8.50]
Percentage (median [IQR])	78.3 [70.0, 85.0]	72.0 [63.2, 79.8]	79.4 [71.8, 85.8]
Percentage > 78—no./total no. (%)	1196/2345 (51.0)	116/388 (29.9)	1080/1957 (55.2)
Lymphocyte			
Count (× 10^3/μL) (median [IQR])	0.90 [0.60, 1.30]	1.10 [0.80, 1.40]	0.90 [0.60, 1.20]
Percentage (median [IQR])	12.3 [7.90, 19.0]	17.4 [11.3, 25.0]	11.7 [7.40, 17.6]
Percentage ≤ 12—no./total no. (%)	1242/2345 (53.0)	131/388 (33.8)	1111/1957 (56.8)
Hemoglobin (g/dL) (median [IQR])	13.3 [11.97, 14.5]	13.8 [12.7, 14.9]	13.2 [11.8, 14.5]
< 12 g/dL—no./total no. (%)	1626/2204 (73.8)	273/321 (85.0)	1353/1883 (71.9)
Platelet count (× 10^3/μL) (median [IQR])	211.0 [160.8, 272.3]	204.0 [164.0, 268.0]	211.0 [160.0, 273.0]
> 200 × 10^3/μL—no./total no. (%)	1299/2344 (55.4)	208/385 (54.0)	1091/1959 (55.7)
eGFR (mL/min/1.73m^2) (median [IQR])	68.8 [40.1, 94.3]	78.1 [57.28, 99.6]	66.3 [37.3, 93.40]
> 60 mL/min/1.73m^2—no./total no. (%)	2505/4295 (58.3)	490/687 (71.3)	2015/3608 (55.8)
30–60 mL/min/1.73m^2—no./total no. (%)	1023/4295 (23.8)	139/687 (20.2)	884/3608 (24.5)
< 30 mL/min/1.73m^2—no./total no. (%)	767/4295 (17.9)	58/687 (8.4)	709/3608 (19.7)
Alanine aminotransferase (U/L) (median [IQR])	30.0 [19.0, 51.0]	29.0 [19.0, 46.0]	30.0 [19.0, 52.0]
> 40 U/L—no./total no. (%)	1370/4009 (34.2)	146/490 (29.8)	1224/3519 (34.8)
Aspartate aminotransferase (U/L) (median [IQR])	43.0 [29.0, 69.0]	35.0 [24.0, 54.0]	44.0 [29.0, 71.0]
> 40 U/L—no./total no. (%)	2111/3952 (53.4)	187/458 (40.8)	1924/3494 (55.1)
C-reactive protein (mg/L) (median [IQR])	125.4 [60.3, 215.3]	89.1 [37.1, 159.6]	127.8 [62.1, 218.9]
> 150 mg/L—no./total no. (%)	623/1491 (41.8)	34/109 (31.2)	589/1382 (42.6)
Procalcitonin (ng/mL) (median [IQR])	0.20 [0.08, 0.65]	0.10 [0.05, 0.31]	0.21 [0.08, 0.68]

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Table 1. (continued)

	Total (n = 6493)	Ambulatory (n = 2785)	Hospitalized (n = 3708)
> 0.5 ng/mL—no./total no. (%)	3143/3143 (100.0)	212/212 (100.0)	2931/2931 (100.0)
Ferritin (ng/mL) (median [IQR])	748 [339, 1769]	518.0 [259, 1347]	759 [351, 1797]
> 400 ng/mL—no./total no. (%)	2278/3234 (70.4)	128/221 (57.9)	2150/3013 (71.4)
Interleukin-6, serum (pg/mL) (median [IQR])	68.2 [32.8, 145.8]	37.4 [21.2, 57.3]	68.5 [33.0, 146.1]
> 100 pg/mL—no./total no. (%)	414/1150 (36.0)	3/13 (23.1)	411/1137 (36.1)
Lactate dehydrogenase (U/L) (median [IQR])	429.0 [322.0, 583.0]	361.5 [282.0, 488.0]	435.0 [326.0, 585.5]
> 440 U/L—no./total no. (%)	1495/3143 (47.6)	66/212 (31.1)	1429/2931 (48.8)
Fibrinogen (mg/dL) (median [IQR])	633.0 [512.0, 755.0]	595.0 [486.5, 691.5]	634.0 [512.3, 758.0]
> 400 mg/dL—no./total no. (%)	1540/1705 (90.3)	52/55 (94.5)	1488/1650 (90.2)
D-dimer (μg/mL) (median [IQR])	1.53 [0.85, 3.01]	1.12 [0.61, 2.29]	1.56 [0.88, 3.04]
> 2 μg/mL—no./total no. (%)	1172/2984 (39.3)	59/214 (27.6)	1113/2770 (40.2)
Troponin (ng/dL) (median [IQR])	0.03 [0.02, 0.10]	0.02 [0.01, 0.05]	0.03 [0.02, 0.10]
> 0.03 ng/dL—no./total no. (%)	1397/2805 (49.8)	85/279 (30.5)	1312/2526 (51.9)
Medications—no./total no. (%)			
Hydroxychloroquine	2863/6493 (44.1)	50/2785 (1.8)	2813/3708 (75.9)
Azithromycin	2785/6493 (42.9)	193/2785 (6.9)	2592/3708 (69.9)
Death (median [IQR])	858/6493 (13.2)	52/2785 (1.9)	806/3708 (21.7)

IQR, interquartile range; WBC, white blood cell count; eGFR, estimated glomerular filtration rate

to have coexisting medical conditions including asthma, chronic obstructive pulmonary disease (COPD), hypertension, obesity, diabetes mellitus (DM), chronic kidney disease (CKD), and cancer. Hospitalized patients were more likely to have abnormal vital signs and abnormal laboratory values including higher WBC count, lymphocyte, and neutrophil counts, higher levels of AST, CRP, procalcitonin, ferritin, IL-6, LDH, D-dimer, and troponin, and lower levels of eGFR and hemoglobin. Clinical characteristics of hospitalized patients stratified by age group, gender, race, and hydroxychloroquine use are shown in Supplementary Tables 2, 3, 4, and 5, respectively.

Survivors and Non-Survivors

Clinical characteristics of the 2014 survivors and 806 non-survivors in the hospitalized group are shown in Table 2 (Supplementary Table 1 for the ambulatory group). The median number of days to discharge for survivors was 5 days (IQR, 3 to 9 days). The median number of days to death for non-survivors was also 5 days (IQR, 3 to 9 days). Compared with survivors, non-survivors were older and the higher proportion were male. Non-survivors were more likely to have a history of cigarette use and coexisting medical conditions including COPD, hypertension, DM, and CKD.

Temporal changes of vital signs and laboratory values in survivors and non-survivors during hospitalization are shown in Figure 1. Throughout hospitalization, non-survivors had higher heart rate and respiratory rate and lower oxygen saturation compared with survivors. Initial laboratory findings of non-survivors demonstrated higher WBC count and higher levels of D-dimer, IL-6, AST, CRP, procalcitonin, ferritin, LDH, fibrinogen, and troponin. Throughout hospitalization, non-survivors had higher WBC count, neutrophil proportion, LDH, and ferritin levels, and lower eGFR and lymphocyte proportion. Non-survivors also had higher levels of CRP, D-dimer, and IL-6 in the first week of hospitalization. Non-survivors showed a marked increase in LDH, CRP, D-dimer, AST, ALT, and procalcitonin on day 1 after admission. Both groups had a trend of decreasing hemoglobin levels and increasing platelet counts during hospitalization; however, a more pronounced decrease in hemoglobin levels was seen in non-survivors, while an increase in platelet counts was greater for survivors. The generalized additive models demonstrated correlations between laboratory values and increased odds of in-hospital mortality which are similar to the difference observed between hospitalized survivors and non-survivors (Supplementary Figure 3).

Treatment

The majority of hospitalized patients received hydroxychloroquine (74.6% of survivors and 71.3% of non-survivors) and azithromycin (67.4% of survivors and 71.3% of non-survivors). Fewer hospitalized patients received other medications such as remdesivir, anakinra, tocilizumab, or sarilumab (Table 2). The majority of ambulatory patients did not receive hydroxychloroquine or azithromycin. Kaplan-Meier estimate showed lower mortality in hospitalized patients who received hydroxychloroquine (log rank P value < 0.001) (Supplementary Figure 4).

Risk Factors Associated with Mortality in Hospitalized Patients

The results of multivariate Cox proportional hazard regression models are shown in Table 3 (univariate models are shown in Supplementary Table 6). Of 3708 hospitalized patients, 888 patients remained hospitalized as of April 7 and were not included in the analysis. In the multivariate analysis, factors associated with a higher risk of in-hospital mortality included age over 50, systolic blood pressure less than 90 mmHg, a respiratory rate greater than 24 per min, SpO_2less than 92%, eGFR less than 60 mL/min/1.73m^2, IL-6 greater than 100 pg/

Table 2 Clinical Characteristics of the Hospitalized Patients with COVID-19

	Survivors (n = 2014)	Non-survivors (n = 806)	In-hospital (n = 888)
Demographics			
Age (median [IQR])	62 [49, 73]	76 [65, 85]	68 [58, 78]
Age—no./total no. (%)			
Age < 50 years old	505/2014 (25.1)	30/806 (3.7)	103/888 (11.6)
Age: 60–79 years old	1086/2014 (53.9)	343/806 (42.6)	486/888 (54.7)
Age ≥ 75 years old	423/2014 (21.0)	433/806 (53.7)	299/888 (33.7)
Female—no./total no. (%)	886/2014 (44.0)	323/806 (40.1)	384/888 (43.2)
Race—no./total no. (%)			
White	496/2014 (24.6)	243/806 (30.1)	189/888 (21.3)
African American	502/2014 (24.9)	194/806 (24.1)	218/888 (24.5)
Asian	81/2014 (4.0)	36/806 (4.5)	39/888 (4.4)
Others	935/2014 (46.4)	333/806 (41.3)	442/888 (49.8)
Ethnicity—no./total no. (%)			
Non-Hispanic	1180/2014 (58.6)	502/806 (62.3)	509/888 (57.3)
Hispanic	594/2014 (29.5)	171/806 (21.2)	252/888 (28.4)
Unknown	240/2014 (11.9)	133/806 (16.5)	127/888 (14.3)
History of cigarette use—no./total no. (%)	455/2014 (22.6)	229/806 (28.4)	225/888 (25.3)
Body mass index (kg/m^2) (median [IQR])	28.07 [24.6, 32.6]	27.6 [23.9, 32.5]	27.5 [24.0, 32.61]
Body mass index ≥ 30 kg/m^2—no./total no. (%)	678/1828 (37.1)	237/662 (35.8)	283/790 (35.8)
Past medical history—no./total no. (%)			
Asthma	97/2014 (4.8)	31/806 (3.8)	45/888 (5.1)
Chronic pulmonary obstructive disease	60/2014 (3.0)	46/806 (5.7)	44/888 (5.0)
Hypertension	606/2014 (30.1)	324/806 (40.2)	342/888 (38.5)
Obesity	164/2014 (8.1)	57/806 (7.1)	67/888 (7.5)
Diabetes	436/2014 (21.6)	221/806 (27.4)	244/888 (27.5)
Chronic kidney disease	186/2014 (9.2)	131/806 (16.3)	114/888 (12.8)
Human immunodeficiency virus infection	38/2014 (1.9)	11/806 (1.4)	15/888 (1.7)
Cancer	125/2014 (6.2)	69/806 (8.6)	60/888 (6.8)
Vital signs—no./total no. (%)			
Temperature ≥ 39 °C	536/2014 (26.6)	294/805 (36.5)	272/888 (30.6)
Peripheral oxygen saturation (SpO_2)			
> 92%	1700/1978 (85.9)	518/705 (73.5)	580/818 (70.9)
88–92%	204/1978 (10.3)	121/705 (17.2)	138/818 (16.9)
≤ 87%	74/1978 (3.7)	66/705 (9.4)	100/818 (12.2)
Heart rate > 120 beats per min	205/2014 (10.2)	97/806 (12.0)	121/888 (13.6)
Respiratory rate			
≤ 24 per min	1847/2014 (91.7)	605/806 (75.1)	653/888 (73.5)
25–30 per min	105/2014 (5.2)	104/806 (12.9)	145/888 (16.3)
> 30 per min	62/2014 (3.1)	97/806 (12.0)	90/888 (10.1)
Systolic blood pressure < 90 mmHg	33/2008 (1.6)	36/804 (4.5)	26/884 (2.9)
Diastolic blood pressure < 60 mmHg	227/2008 (11.3)	158/804 (19.7)	124/884 (14.0)
Laboratory results			
WBC (× 10^3/μL) (median [IQR])	7.00 [5.30, 9.41]	8.80 [6.19, 12.2]	8.30 [5.80, 11.9]
< 4.0 × 10^3/μL—no./total no. (%)	172/1967 (8.7)	47/796 (5.9)	55/887 (6.2)
4.0–8.0 × 10^3/μL—no./total no. (%)	1545/1967 (78.5)	542/796 (68.1)	621/887 (70.0)
> 12.0 × 10^3/μL—no./total no. (%)	250/1967 (12.7)	207/796 (26.0)	211/887 (23.8)
Neutrophil			
Count (× 10^3/μL) (median [IQR])	5.20 [3.60, 7.50]	7.10 [4.90, 10.5]	6.30 [4.20, 9.30]
Percentage (median [IQR])	77.7 [70.0, 84.1]	81.8 [74.0, 87.7]	82.0 [75.2, 87.1]
Percentage > 78—no./total no. (%)	533/1103 (48.3)	249/393 (63.4)	298/461 (64.6)
Lymphocyte			
Count (× 10^3/μL) (median [IQR])	0.90 [0.70, 1.30]	0.80 [0.50, 1.10]	0.80 [0.50, 1.10]
Percentage (median [IQR])	13.0 [8.60, 19.2]	9.20 [5.70, 15.0]	10.1 [6.30, 15.5]
Percentage ≤ 12—no./total no. (%)	542/1103 (49.1)	266/393 (67.7)	303/461 (65.7)
Hemoglobin (g/dL) (median [IQR])	13.4 [12.2, 14.5]	12.9 [11.1, 14.4]	13.4 [11.6, 14.4]
< 12 g/dL—no./total no. (%)	708/903 (78.4)	313/506 (61.9)	332/474 (70.0)
Platelet count (× 10^3/μL) (median [IQR])	212.0 [166.0, 267.0]	197.0 [146.0, 252.0]	225.0 [164.0, 296.0]
> 200 × 10^3/μL—no./total no. (%)	629/1105 (56.9)	184/393 (46.8)	278/461 (60.3)
eGFR (mL/min/1.73m^2) (median [IQR])	76.8 [49.5, 102.0]	45.8 [24.3, 70.7]	61.4 [32.5, 89.6]
> 60 mL/min/1.73m^2—no./total no. (%)	1289/1925 (67.0)	264/796 (33.2)	462/887 (52.1)
30–60 mL/min/1.73m^2—no./total no. (%)	383/1925 (19.9)	282/796 (35.4)	219/887 (24.7)
< 30 mL/min/1.73m^2—no./total no. (%)	253/1925 (13.1)	250/796 (31.4)	206/887 (23.2)
Alanine aminotransferase (U/L) (median [IQR])	29.0 [18.0, 52.0]	32.0 [20.0, 54.0]	29.0 [18.0, 53.0]
> 40 U/L—no./total no. (%)	634/1869 (33.9)	288/773 (37.3)	302/877 (34.4)
Aspartate aminotransferase (U/L) (median [IQR])	40.0 [28.0, 62.0]	56.0 [35.0, 90.0]	46.0 [31.0, 73.0]
> 40 U/L—no./total no. (%)	891/1856 (48.0)	522/762 (68.5)	511/876 (58.3)
C-reactive protein (mg/L) (median [IQR])	93.9 [44.6, 172.7]	174.4 [95.3, 254.6]	154.04 [82.7, 239.5]
> 150 mg/L—no./total no. (%)	203/657 (30.9)	178/315 (56.5)	208/410 (50.7)
Procalcitonin (ng/mL) (median [IQR])	0.13 [0.06, 0.37]	0.47 [0.18, 1.53]	0.27 [0.11, 0.82]
> 0.5 ng/mL—no./total no. (%)	1545/1545 (100.0)	581/581 (100.0)	805/805 (100.0)
Ferritin (ng/mL) (median [IQR])	637.5 [287.8, 1479.0]	938.0 [432.0, 2186.0]	928.0 [434.0, 2051.5]
> 400 ng/mL—no./total no. (%)	1017/1556 (65.4)	490/625 (78.4)	643/832 (77.3)
Interleukin-6, serum (pg/mL) (median [IQR])	45.8 [23.3, 82.4]	152.4 [79.1, 303.8]	78.4 [40.7, 152.1]
> 100 pg/mL—no./total no. (%)	117/582 (20.1)	187/287 (65.2)	107/268 (39.9)

(continued on next page)

Table 2. (continued)

	Survivors (n = 2014)	Non-survivors (n = 806)	In-hospital (n = 888)
Lactate dehydrogenase (U/L) (median [IQR])	391.0 [303.0, 500.0]	511.0 [382.0, 758.0]	478.0 [364.0, 650.0]
>440 U/L—no./total no. (%)	586/1545 (37.9)	372/581 (64.0)	471/805 (58.5)
Fibrinogen (mg/dL) (median [IQR])	616.0 [506.0, 727.0]	634.0 [506.0, 777.0]	664.0 [521.8, 790.0]
> 400 mg/dL—no./total no. (%)	696/761 (91.5)	302/349 (86.5)	490/540 (90.7)
D-dimer (μg/mL) (median [IQR])	1.25 [0.73, 2.35]	2.29 [1.29, 4.00]	1.79 [1.05, 3.51]
> 2 μg/mL—no./total no. (%)	426/1407 (30.3)	315/548 (57.5)	372/815 (45.6)
Troponin (ng/dL) (median [IQR])	0.02 [0.01, 0.06]	0.07 [0.03, 0.21]	0.04 [0.02, 0.12]
> 0.03 ng/dL—no./total no. (%)	410/1108 (37.0)	504/718 (70.2)	398/700 (56.9)
Interleukin-1b (pg/mL) (median [IQR])	0.50 [0.30, 0.80]	0.60 [0.40, 1.20]	0.50 [0.40, 0.80]
> 5 pg/mL—no./total no. (%)	6/354 (1.7)	0/100 (0.0)	2/168 (1.2)
Interleukin-8 (pg/mL) (median [IQR])	34.6 [22.2, 54.6]	60.2 [37.9, 112.5]	46.2 [32.0, 75.2]
> 5 pg/mL—no./total no. (%)	423/424 (99.8)	115/115 (100.0)	197/198 (99.5)
Tumor necrosis factor alpha (pg/mL) (median [IQR])	20.60 [15.9, 28.3]	25.9 [19.7, 38.3]	23.9 [16.7, 36.7]
> 22 pg/mL—no./total no. (%)	194/423 (45.9)	75/115 (65.2)	115/198 (58.1)
Medications			
Treatments			
Hydroxychloroquine—no./total no. (%)	1502/2014 (74.6)	575/806 (71.3)	736/888 (82.9)
Initiation (day) (median [IQR])	0.74 [0.43, 1.15]	0.89 [0.51, 1.65]	0.57 [0.32, 0.96]
Azithromycin—no./total no. (%)	1357/2014 (67.4)	575/806 (71.3)	660/888 (74.3)
Initiation (day) (median [IQR])	0.11 [0.00, 0.45]	0.11 [0.01, 0.49]	0.10 [−0.02, 0.42]
Remdesivir—no./total no. (%)	11/2014 (0.5)	2/806 (0.2)	43/888 (4.8)
Initiation (day) (median [IQR])	4.04 [2.23, 5.56]	4.04 [3.56, 4.53]	2.84 [2.50, 3.66]
Anakinra—no./total no. (%)	0/2014 (0.0)	2/806 (0.2)	1/888 (0.1)
Initiation (day) (median [IQR])	NA	3.67 [3.41, 3.92]	2.13 [2.13, 2.13]
Tocilizumab—no./total no. (%)	47/2014 (2.3)	60/806 (7.4)	57/888 (6.4)
Initiation (day) (median [IQR])	2.25 [1.37, 4.26]	3.16 [2.05, 5.83]	3.61 [1.95, 6.02]
Sarilumab—no./total no. (%)	10/2014 (0.5)	12/806 (1.5)	10/888 (1.1)
Initiation (day) (median [IQR])	4.29 [2.15, 5.19]	5.23 [3.90, 8.06]	3.11 [1.79, 5.67]
Anticoagulation			
Heparin—no./total no. (%)	1233/2014 (61.2)	546/806 (67.7)	486/888 (54.7)
Enoxaparin—no./total no. (%)	766/2014 (38.0)	248/806 (30.8)	581/888 (65.4)
Apixaban—no./total no. (%)	189/2014 (9.4)	106/806 (13.2)	219/888 (24.7)
Rivaroxaban—no./total no. (%)	34/2014 (1.7)	17/806 (2.1)	13/888 (1.5)
Tissue plasminogen activator—no./total no. (%)	4/2014 (0.2)	40/806 (5.0)	36/888 (4.1)
Initiation of anticoagulation (day) (median [IQR])	0.40 [0.20, 0.74]	0.43 [0.24, 0.81]	0.33 [0.15, 0.67]
Other variables			
Length of stay (median [IQR])	5 [3, 9]	5 [3, 10]	NA

IQR, interquartile range; WBC, white blood cell count; eGFR, estimated glomerular filtration rate

mL (6.5 times upper limit of normal [ULN]), D-dimer greater than 2 mcg/mL (4 times ULN), and troponin greater than 0.03 ng/mL. Factors associated with a lower risk of in-hospital mortality included female sex, African American race, and hydroxychloroquine use. The adjustment with IPTW did not lead to a significant change in the HR of hydroxychloroquine (without IPTW: HR 0.53, CI 0.41–0.67; with IPTW: HR 0.53, CI 0.41–0.68).

DISCUSSION

We report a large retrospective cohort study of both ambulatory and hospitalized patients with COVID-19 from across the New York City metropolitan area. The clinical characteristics described here represent the first large retrospective cohort study from the US population in a city at the epicenter of the pandemic.

Early reports showed that COVID-19 had a mortality rate among all confirmed cases of 2%[12] which is significantly lower compared with that of 34% with MERS[13] and 10% with SARS[14]. The mortality rate in hospitalized patients reported previously ranged from 4 to 28%[2, 7–9, 11]. The mortality rate of 25.9% among hospitalized patients in our study may be explained by more severe disease in our total cohort, by a different reporting method, or by geographic variation.

We identified several risk factors associated with mortality in hospitalized patients with COVID-19 that have been previously reported including older age and male sex. We report additional risk factors associated with in-hospital mortality including low SBP, tachypnea, low SpO_2, low eGFR, and higher levels of IL-6, D-dimer, and troponin levels.

The severity of coronavirus infection in humans has been previously described to increase during viral clearance suggesting pathogenicity arising from host immune response[15]. Our study confirmed again that older patients with COVID-19 hospitalization are at significantly higher risk of mortality. We did not observe any independent association between in-hospital mortality and some of the common coexisting medical conditions including hypertension, diabetes, or cancer. However, using calculated GFR as a surrogate for CKD, we observed that decreased renal function was a risk factor for in-hospital mortality, a finding that is consistent with previous studies[16].

IL-6 and other pro-inflammatory cytokines production are felt to be due to immune dysregulation rather than normal

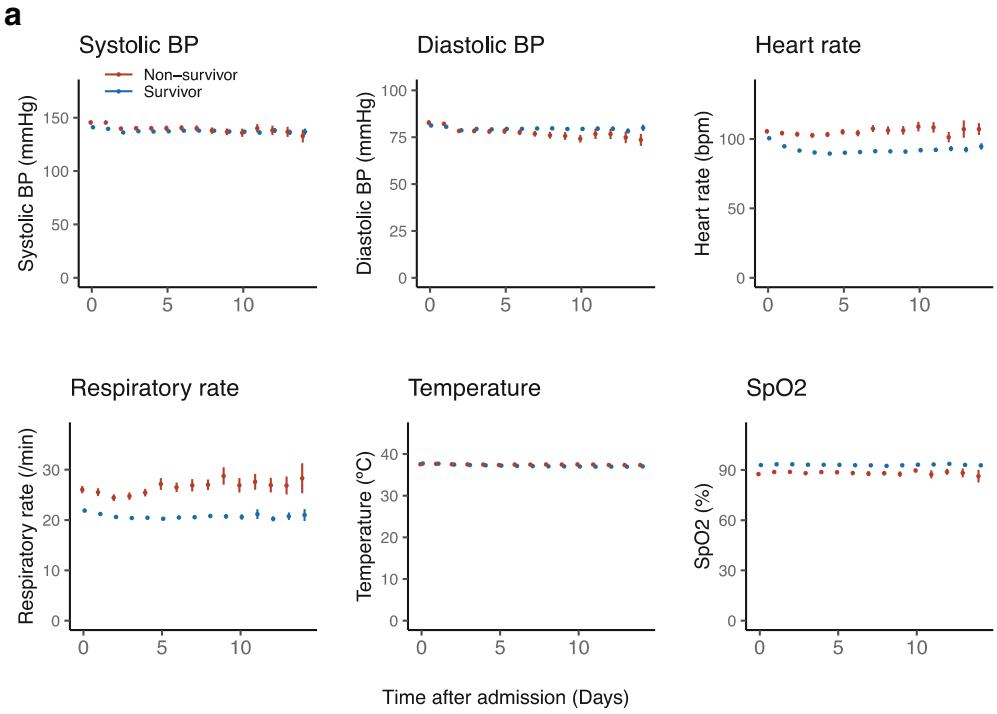

Figure 1 a Temporal change of vital signs in patients with COVID-19. BP, blood pressure; SpO_2, peripheral oxygen saturation. b Temporal change of laboratory values in patients with COVID-19. WBC, white blood cell count; eGFR, estimated glomerular filtration rate; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; IL-6, interleukin-6; LDH, lactate dehydrogenase.

response to SARS-CoV infection[17, 18]. Our findings are consistent with this theory, and we observed elevated IL-6 as an independent prognostic risk factor, with higher levels in non-survivors. In hospitalized patients, we saw fluctuating IL-6 levels, with a significant increase seen on day 1 of admission and an increasing level trend that was more pronounced in non-survivors.

Thrombocytosis was associated with disease activity in SARS and was thought to be secondary to the direct effect of the virus or effect of inflammatory cytokines[19]. We observed a greater thrombocytosis during hospitalization in survivors than in non-survivors. A previous study of IL-6 in primates revealed that there is a dose-dependent response of thrombocytosis induced by IL-6[20]. The discrepancy between high IL-6 levels and lack of thrombocytosis in non-survivors could be explained by endothelial damage and subsequent platelet consumption from viral infection, impaired platelet release from megakaryocytes in the lung, or direct impairment of hematopoiesis[21]. This may suggest that the absence of reactive thrombocytosis may portend a poor response to SARS-CoV-2 infection.

Elevated D-dimer in COVID-19 patients has been described previously[22, 23]. We report in this study its independent association with an increased risk of in-hospital mortality. Abnormal D-dimer alone is non-specific; however, the higher elevation in non-survivors suggests that coagulopathy, particularly disseminated intravascular coagulation (DIC), may contribute to mortality in COVID-19.

One of the functional receptors for pathogenic human coronavirus such as SARS-CoV is angiotensin-converting enzyme 2 (ACE2)[24], and these receptors are expressed in heart tissues[25]. This suggests that SARS-CoV-2 virus could directly affect the heart. Similar to the previous finding that showed an association of cardiac injury and a higher risk of in-hospital mortality[26], we observed elevated troponin levels in hospitalized patients as a risk factor for increased mortality.

Hydroxychloroquine is an analog of chloroquine, a widely used anti-malarial with immunomodulatory effects[27]. In vitro studies have shown that hydroxychloroquine has activity against SARS-CoV-2 [28]. The clinical data of hydroxychloroquine in patients with COVID-19 come from small studies that have shown mixed results. Chen et al. randomized 30 hospitalized patients with COVID-19 to receive hydroxychloroquine 400 mg daily for 5 days or placebo and found that 86.7% of the hydroxychloroquine group and 93.3% of the control group had negative throat swabs[29]. Chen et al. randomized 62 patients to hydroxychloroquine or placebo and reported shortened time to clinical recovery, fever resolution, and cough improvement in the hydroxychloroquine group[30]. Mahevas et al. reviewed 181 hospitalized patients with COVID-19 data who received hydroxychloroquine 600 mg daily and reported no difference in outcomes, including in ICU admission and/or death at 7 days follow-up[31]. Another randomized trial of 150 hospitalized patients by Tang et al. did not show symptomatic improvement at 28 days or clearance of

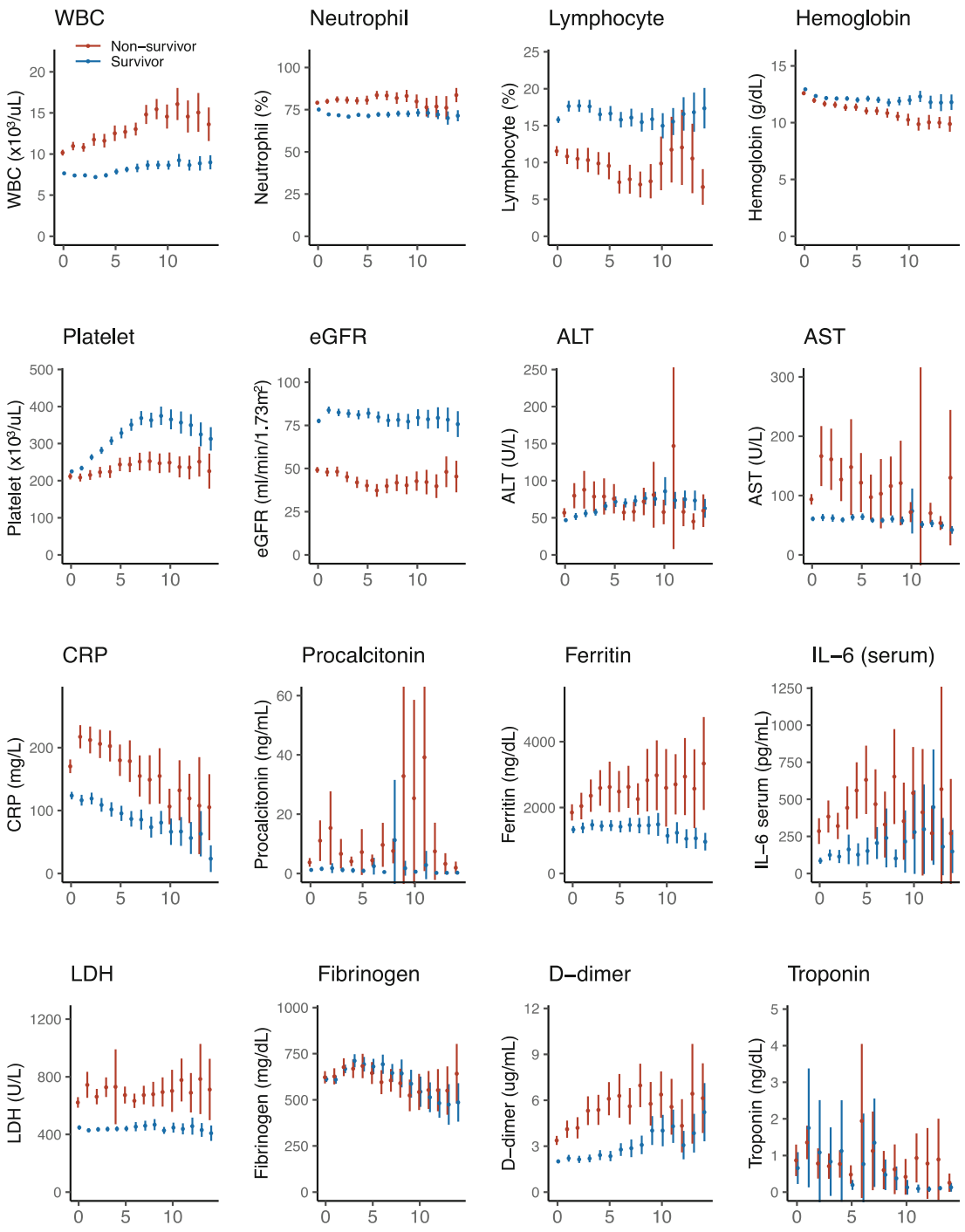

Fig. 1 (continued)

SARS-CoV-2 with hydroxychloroquine use[32]. We attempted to adjust for all known confounders between the groups who did and did not receive hydroxychloroquine using multivariate regression analyses and the IPTW method, which revealed that hydroxychloroquine use was associated with decreased risk of in-hospital mortality. Due to the inherent limitations of our retrospective study design, there was no conclusive determination on the efficacy of hydroxychloroquine in patients with COVID-19. More robust studies such as randomized clinical trials are needed.

Our study has several limitations. First, we have no long-term follow up data for ambulatory and discharged patients; hence, the clinical outcome observed may not be reflective of the true eventual outcome, particularly in the ambulatory group. Second, we have patients who remained hospitalized at the time of our analyses and did not have our outcomes,

Table 3 Risk Factors Associated with In-Hospital Death

	Hazard ratio (95% CI)	*P* value
Age (reference: < 50 years old)		
50–74 years old	2.34 (1.47–3.71)	< 0.001
≥ 75 years old	4.85 (2.75–8.56)	< 0.001
Sex (Female)	0.82 (0.75–0.90)	< 0.001
Race (reference: White)		
African American	0.78 (0.65–0.95)	0.011
Asian	0.94 (0.83–1.08)	0.397
Others	1.00 (0.83–1.19)	0.971
Cigarettes use history (reference: never smoker)	1.01 (0.90–1.13)	0.916
Hypertension	0.91 (0.79–1.07)	0.250
Diabetes	0.92 (0.73–1.16)	0.481
Cancer	1.08 (0.84–1.40)	0.550
Systolic blood pressure < 90 mmHg	1.38 (1.06–1.80)	0.017
Respiratory rate		
25–30 per min	1.43 (1.13–1.83)	0.004
> 30 per min	1.68 (1.19–2.36)	0.003
Peripheral oxygen saturation ≤ 92%	2.12 (1.56–2.88)	< 0.001
Lymphocyte ≤12%	1.12 (0.97–1.29)	0.110
Estimated glomerular filtration rate		
31–60 mL/min/1.73m^2	1.80 (1.60–2.02)	< 0.001
< 30 mL/min/1.73m^2	2.20 (1.83–2.65)	< 0.001
C-reactive protein >150 mg/L	1.03 (0.78–1.36)	0.815
Interleukin-6, serum >100 pg/mL	1.50 (1.12–2.03)	0.007
Lactate dehydrogenase >440 U/L	1.25 (0.86–1.81)	0.240
D-dimer >2 μL/mL	1.19 (1.02–1.39)	0.031
Troponin >0.03 ng/dL	1.41 (1.23–1.62)	< 0.001
Hydroxychloroquine use	0.53 (0.41–0.67)	< 0.001

such as discharge or mortality, and were excluded for our comparison of survivors and non-survivors. Third, due to limitations and local testing policy during the study duration, there are an unknown number of patients who were not diagnosed with COVID-19 because of a lack of severe symptoms and/or hospitalization. Fourth, we are not able to adjust for unknown confounders that may affect the true treatment effect. These limitations prevent any definitive conclusions on the efficacy of any treatment.

CONCLUSIONS

In this retrospective study of over 6000 ambulatory and hospitalized patients with COVID-19 in the New York City metropolitan area, age, male sex, tachypnea, low systolic blood pressure, low peripheral oxygen saturation, impaired renal function, elevated IL-6, elevated D-dimer, and elevated troponin were found to be risk factors for mortality. Hydroxychloroquine use was associated with decreased mortality.

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Authors' Roles: *TM and ES had the idea for and designed the study and had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. TM and ES drafted the paper. TM, ES, HM, and TY did the analysis, and all authors critically revised the manuscript for important intellectual content and gave final approval for the version to be published. TM and ES collected the data. All authors agree to the accuracy or integrity of any part of the work are appropriately investigated and resolved.*

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The Washington Post

The ultimate covid-19 mystery: Why does it spare some and kill others?

Joel Achenbach, Karin Brulliard, Ariana Eunjung Cha 3 hrs ago

The novel coronavirus can be a killer — or no big deal. It can put a person in the intensive care unit on a ventilator, isolated from family, facing a lonely death — or it can come and go without leaving a mark, a ghost pathogen, more rumor than reality.

© Ciro Fusco/EPA-EFE/REX/Shutterstock Commuters arrive at the Naples Central Stationon June 3, 2020 after the reopening of regional borders amid an easing of restrictions during Phase 2 of the coronavirus emergency in Italy.

Six months into a pandemic that has killed more than 400,000 people globally, scientists are still trying to understand the wildly variable nature of covid-19, the disease caused by the virus.

Among their lines of inquiry: Are distinct strains of the coronavirus more dangerous? Does a patient's blood type affect the severity of the illness? Do other genetic factors play a role? Are some people partially protected from covid-19 because they've had recent exposure to other coronaviruses?

Much of the research remains provisional or ambiguous, and for now scientists can't do much better than say that covid-19 is more likely to be worse for older people — often described as over the age of 60 — and for those with chronic conditions such as hypertension, diabetes, lung disease and heart disease.

That describes tens of millions of people in the United States alone. It also isn't much of an explanation: The link between chronic disease and the severity of covid-19 is more in the category of correlation than causation. The "why" of the matter remains unclear.

The issue of disease variability "is the most critical question about covid," said Edward Behrens, chief of the rheumatology division at Children's Hospital of Philadelphia.

"Why do some people get sick? Why do some people have no problem at all?" he said.

Social and demographic factors, including sex, race, ethnicity, income and access to quality health care, play major roles in how this pandemic affects people and who suffers the most. The ultimate goal of many researchers is to develop a personalized risk score — so that a person who has covid-19, or remains vulnerable to catching the disease, would have some idea of how to navigate the pandemic.

Blood markers

One potential breakthrough was highlighted by National Institutes of Health Director Francis Collins on his blog: Scientists developed an artificial intelligence tool that sorted the blood of covid-19 patients and found 22 proteins that consistently appear among the patients who are severely ill.

At this point, such a blood marker only tells doctors what they can already see with their own eyes — a very sick patient. But if such a blood test and analysis could be rolled out early in the course of the disease, it could help doctors decide which patients are most vulnerable.

Blood-type research is also intriguing. This month, European scientists posted online a study — not yet peer-reviewed — that found strong links between variations on two places in the genome and respiratory failure in covid-19 patients in Italy and Spain.

One, the ABO gene, determines blood type. The researchers found that patients who had Type A blood had a 50 percent higher risk of needing oxygen or a ventilator. Type O blood seemed to have a partial protective effect.

Why that gene matters remains unknown, according to co-author Andre Franke, a professor of molecular medicine at the University of Kiel in Germany. The genetic variant may cause the risk by being associated with inflammation.

Another possibility is that Type A blood is associated with small blood clots that characterize some severe covid-19 cases. And "there may be other things cooking in that region" of the genome, Franke said.

The consumer genetics giants Ancestry.com and 23andMe are getting involved. 23andMe recently released preliminary findings showing that people with Type O blood are 9 to 18 percent less likely to test positive for covid-19 than people with

More than 750,000 of the company's customers have completed a web-based survey about their experiences with covid-19, and 2,000 of them said they'd been hospitalized from the disease. The company is now recruiting 10,000 non-customers who have been hospitalized with covid-19.

"It would be very nice if there was a single gene that we could understand as conferring different levels of risk for covid-19," said Adam Auton, 23andMe's principal scientist. "In reality, dozens or hundreds or even thousands of genes are all making very small contributions toward disease risk."

Jean-Laurent Casanova, head of the St. Giles Laboratory of Human Genetics of Infectious Diseases at Rockefeller University, is co-leading an international team searching the genomes of "outliers" — patients younger than 50 who had no known preexisting conditions, but were hospitalized with life-threatening cases of covid-19. They're looking for unusual gene variants that these patients have in common.

Casanova and his colleagues have previously found genetic mutations that increase a person's susceptibility to infectious diseases, such as severe pneumonia caused by influenza.

"There are many, many infectious diseases for which genetic variations have been shown to be causal," Casanova said. "So when covid occurred, if I may say, it's business as usual."

Video: Why covid-19 isn't going away anytime soon

How the virus infects you — and how much

Numerous papers have explored whether different strains of the virus are more transmissible or lethal. One strain has become dominant in much of Europe and the United States. That strain has a genetic mutation affecting what is called the spike protein — the structure that lets the virus bind to receptor cells in humans.

So far, there is no consensus that this or other mutations are significant from a clinical standpoint. Collins, the NIH director, says of the different strains, "I think they're all acting the same."

Another possibility frequently discussed by researchers is that the mode of transmission is key to understanding the severity of the disease. Many scientists argue that, contrary to what the World Health Organization and the Centers for Disease Control and Prevention have repeatedly stated, the virus sometimes spreads through tiny aerosol particles, not simply through large respiratory droplets.

That leads some scientists to think the aerosol transmission could enable the virus to penetrate deep into the lungs and trigger a more severe infection.

The body has an "innate immune system" that includes physical obstacles for any invading viruses. But tiny particles can go with the air flow and potentially reach the deepest regions of the lungs, said Raymond Tellier, a microbiologist at McGill University Health Center.

For Tellier, that's a sign that this virus must be spreading in part through aerosols.

"How else would the virus go down the lower respiratory tract where the cells can be infected?" he asks.

The amount of virus initially transmitted from one person to another could play a role in determining the course of illness: more virus, sicker patients. Albert Ko, an infectious-disease epidemiologist at the Yale School of Public Health, said, "If I spew out a lot of virus at you and you're one foot away, you're going to get a higher inoculum than if you're six feet away."

Immune system idiosyncrasies

Even with all the focus on the virus, and its potential mutations and dosages, the most critical factor is the person getting infected — the "host." Not everyone hosts the virus the same way. The human immune system is "a complicated tangle of pathways and partners," as Collins puts it.

It's conceivable, Collins said, that some people have immune systems that are better primed for this new invader because of previous exposure to genetically related coronaviruses. That's still highly conjectural.

The immune system not only can be protective, it can also go haywire and make an illness catastrophically worse. If the immune system is an army that attacks infections, molecules called cytokines are the messengers that tell the troops what to do to beat back the invader. Too few cytokines, and the defense will be too weak, allowing the infection to progress. Too many, and the commands become a cacophony that causes an erratic and overreactive immune response — a cytokine storm.

"The army goes crazy and just sort of does more damage than they would intend to do," said Behrens, of Children's Hospital of Philadelphia.

"You start making too many cytokines all at the same time. Now your immune cells are confused. They're trying to do everything all at once," he said. "Now it's no longer the virus that's killing you, it's the immune system that's killing you."

Some children infected with the coronavirus have a severe, sometimes fatal Kawasaki-like syndrome. It affects multiple organs — "the gut, the heart, the skin, the eyes," Behrens said — and research by his team suggests it is a cytokine storm. Behrens hopes the team's study of children with covid-19 will also shed light on why some adults get so sick.

Quickly identifying a storm of cytokines, which can be detected in blood tests, is key, he said. In March, CHOP developed a rapid diagnostic test, which delivers patients' results in a day. But there's much more to learn.

"What is their particular storm? Where in the process are they? Which drug should we pull off the shelf?" Behrens said. "That kind of personalized precision medicine is the holy grail for all this."

Obesity

In the United Kingdom, health officials have released two different measures of risk. One developed by the National Health Service looks at age, gender and very granular medical factors such as whether you have preexisting conditions such as high blood pressure or diabetes.

Those at low risk are asked to social distance as the economy reopens. Those at higher risk are asked to “shield,” which means staying inside as much as possible and avoiding contact with others.

Jennifer Lighter, a hospital epidemiologist at NYU Langone, found that obesity was the No. 1 risk factor in her hospital system among those younger than 60. Patients with a body mass index between 30 and 34 — obese under CDC definitions — were two times as likely to be admitted to the ICU than patients with a BMI under 30. Those with a BMI of 35 and over were three times more likely to die than those with a healthy BMI.

“As we are opening up the nation, one idea is to consider opening up by risk groups,” Lighter said.

In the broadest sense, the risk of a bad outcome is pretty clear. It’s better to be young and healthy if the coronavirus pays a visit.

Among the 238 sailors aboard the aircraft carrier USS Theodore Roosevelt who tested positive for the virus after an outbreak on the ship, only two required hospitalization, according to a new study from the CDC. One out of 5 reported no symptoms at all.

Older people suffer from immunosenescence. Their immune systems become “dysregulated.” Casanova describes this as “the inevitable descending slope of life from about the age of 18 or 19.”

The median age of people who died in virus-ravaged northern Italy was 81.

“The difference between catching covid and dying is so stark the older you get, it’s important to recognize that,” said Carl Heneghan, director of the Center for Evidence-Based Medicine at Oxford University. In the U.K., there’s been “virtually no excess death” for people under age 45 since the pandemic began, he said.

Another wrinkle: People who have little history of viral infections tend to have more severe reactions when they get infected later in life.

“You have to try and stay healthy, get fit,” Heneghan said. “If you’ve got diabetes, you’ve got to lose weight and moderate that. If you do all those things, your risk of dying is small, or very small.”

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Coronavirus May Be a Blood Vessel Disease, Which Explains Everything

Many of the infection's bizarre symptoms have one thing in common

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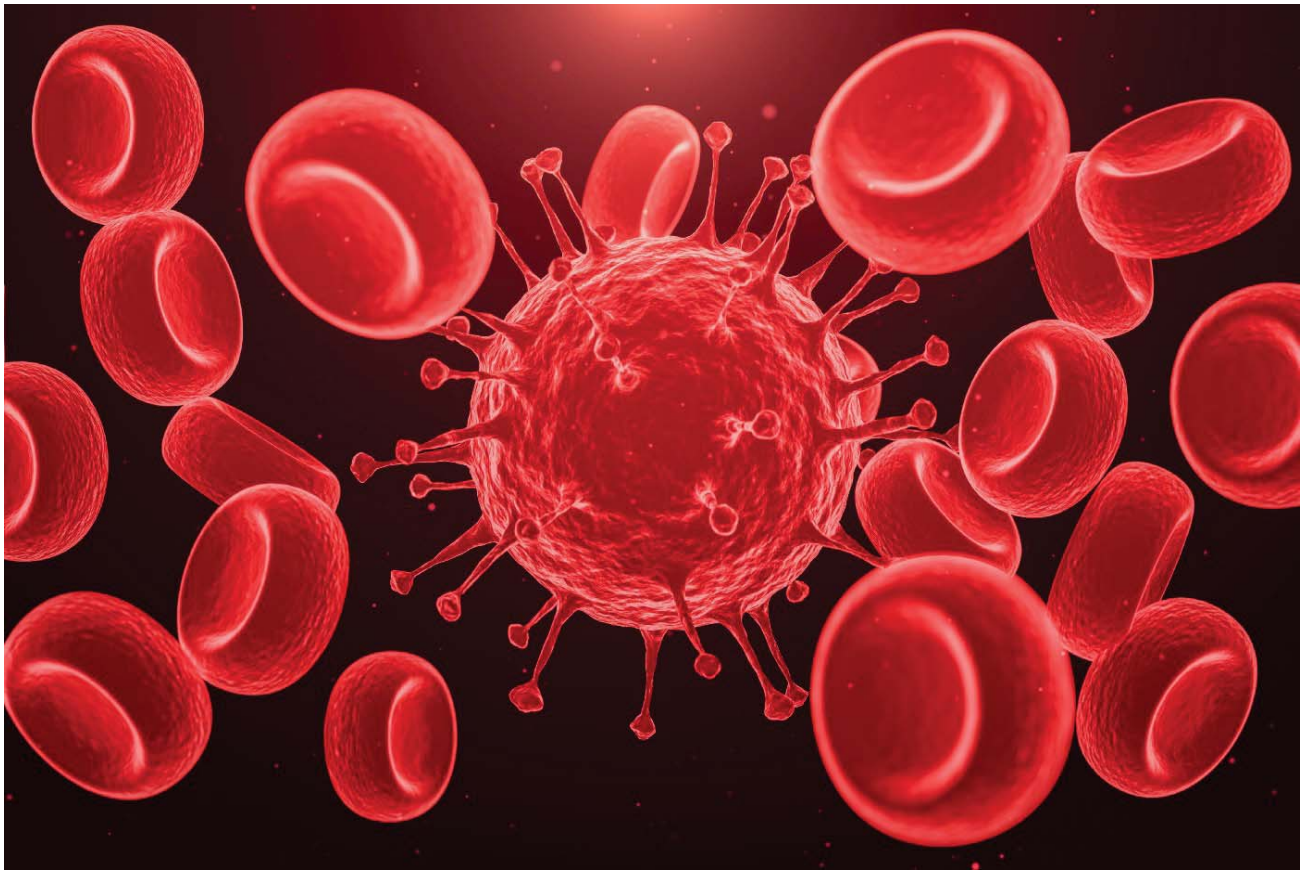

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In April, blood clots emerged as one of the many mysterious symptoms attributed to Covi 19, a disease that had initially been thought to largely affect the lungs in the form of pneumonia. Quickly after came reports of young people dying due to coronavirus-related strokes. Next it was Covid toes — painful red or purple digits.

What do all of these symptoms have in common? An impairment in blood circulation. Add in the fact that 40% of deaths from Covid-19 are related to cardiovascular complications, and the disease starts to look like a vascular infection instead of a purely respiratory one.

Months into the pandemic, there is now a growing body of evidence to support the theory that the novel coronavirus can infect blood vessels, which could explain not only the high prevalence of blood clots, strokes, and heart attacks, but also provide an answer for the diverse set of head-to-toe symptoms that have emerged.

Every Covid-19 Symptom We Know About Right Now, From Head to Toe

The most perplexing things about a disease that has proved vexing, deadly, and 'unprecedented in many ways'

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"All these Covid-associated complications were a mystery. We see blood clotting, we see kidney damage, we see inflammation of the heart, we see stroke, we see encephalitis [swelling of the brain]," says William Li, MD, president of the Angiogenesis Foundation. "A whole myriad of seemingly unconnected phenomena that you do not normally see with SARS or H1N1 or, frankly, most infectious diseases."

"If you start to put all of the data together that's emerging, it turns out that this virus is probably a vasculotropic virus, meaning that it affects the [blood vessels]," says Mandeep Mehra, MD, medical director of the Brigham and Women's Hospital Heart and Vascular Center.

In a paper published in April in the scientific journal *The Lancet*, Mehra and a team of scientists discovered that the SARS-CoV-2 virus can infect the endothelial cells that line the inside of blood vessels. Endothelial cells protect the cardiovascular system, and they release proteins that influence everything from blood clotting to the immune response.

In the paper, the scientists showed damage to endothelial cells in the lungs, heart, kidneys, liver, and intestines in people with Covid-19.

“The concept that’s emerging is that this is not a respiratory illness alone, this is a respiratory illness to start with, but it is actually a vascular illness that kills people through its involvement of the vasculature,” says Mehra.

> A respiratory virus infecting blood cells and circulating through the body is virtually unheard of.

A one-of-a-kind respiratory virus

SARS-CoV-2 is thought to enter the body through ACE2 receptors present on the surface of cells that line the respiratory tract in the nose and throat. Once in the lungs, the virus appears to move from the alveoli, the air sacs in the lung, into the blood vessels, which are also rich in ACE2 receptors.

“[The virus] enters the lung, it destroys the lung tissue, and people start coughing. The destruction of the lung tissue breaks open some blood vessels,” Mehra explains. “Then it starts to infect endothelial cell after endothelial cell, creates a local immune response, and inflames the endothelium.”

A respiratory virus infecting blood cells and circulating through the body is virtually unheard of. Influenza viruses like H1N1 are not known to do this, and the original SARS virus, a sister coronavirus to the current infection, did not spread past the lung. Other types of viruses, such as Ebola or Dengue, can damage endothelial cells, but they are very different from viruses that typically infect the lungs.

Why Lying Face-Down Helps Relieve Coronavirus Symptoms

How ‘proning’ Covid-19 patients helps them breathe

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Benhur Lee, MD, a professor of microbiology at the Icahn School of Medicine at Mount Sinai, says the difference between SARS and SARS-CoV-2 likely stems from an extra

protein each of the viruses requires to activate and spread. Although both viruses dock onto cells through ACE2 receptors, another protein is needed to crack open the virus so its genetic material can get into the infected cell. The additional protein the original SARS virus requires is only present in lung tissue, but the protein for SARS-CoV-2 to activate is present in all cells, especially endothelial cells.

"In SARS1, the protein that's required to cleave it is likely present only in the lung environment, so that's where it can replicate. To my knowledge, it doesn't really go systemic," Lee says. "[SARS-CoV-2] is cleaved by a protein called furin, and that's a big danger because furin is present in all our cells, it's ubiquitous."

Endothelial damage could explain the virus' weird symptoms

An infection of the blood vessels would explain many of the weird tendencies of the novel coronavirus, like the high rates of blood clots. Endothelial cells help regulate clot formation by sending out proteins that turn the coagulation system on or off. The cells also help ensure that blood flows smoothly and doesn't get caught on any rough edges on the blood vessel walls.

"The endothelial cell layer is in part responsible for [clot] regulation, it inhibits clot formation through a variety of ways," says Sanjum Sethi, MD, MPH, an interventional cardiologist at Columbia University Irving Medical Center. "If that's disrupted, you could see why that may potentially promote clot formation."

Endothelial damage might account for the high rates of cardiovascular damage and seemingly spontaneous heart attacks in people with Covid-19, too. Damage to endothelial cells causes inflammation in the blood vessels, and that can cause any plaque that's accumulated to rupture, causing a heart attack. This means anyone who has plaque in their blood vessels that might normally have remained stable or been controlled with medication is suddenly at a much higher risk for a heart attack.

"Inflammation and endothelial dysfunction promote plaque rupture," Sethi says. "Endothelial dysfunction is linked towards worse heart outcomes, in particular myocardial infarction or heart attack."

Blood vessel damage could also explain why people with pre-existing conditions like high blood pressure, high cholesterol, diabetes, and heart disease are at a higher risk for

severe complications from a virus that's supposed to just infect the lungs. All of those diseases cause endothelial cell dysfunction, and the additional damage and inflammation in the blood vessels caused by the infection could push them over the edge and cause serious problems.

The theory could even solve the mystery of why ventilation often isn't enough to help many Covid-19 patients breathe better. Moving air into the lungs, which ventilators help with, is only one part of the equation. The exchange of oxygen and carbon dioxide in the blood is just as important to provide the rest of the body with oxygen, and that process relies on functioning blood vessels in the lungs.

"If you have blood clots within the blood vessels that are required for complete oxygen exchange, even if you're moving air in and out of the airways, [if] the circulation is blocked, the full benefits of mechanical ventilatory support are somewhat thwarted," says Li.

A new paper published last week in the *New England Journal of Medicine,* on which Li is a co-author, found widespread evidence of blood clots and infection in the endothelial cells in the lungs of people who died from Covid-19. This was in stark contrast to people who died from H1N1, who had nine times fewer blood clots in the lungs. Even the structure of the blood vessels was different in the Covid-19 lungs, with many more new branches that likely formed after the original blood vessels were damaged.

"We saw blood clots everywhere," Li says. "We were observing virus particles filling up the endothelial cell like filling up a gumball machine. The endothelial cell swells and the cell membrane starts to break down, and now you have a layer of injured endothelium."

Finally, infection of the blood vessels may be how the virus travels through the body and infects other organs — something that's atypical of respiratory infections.

"Endothelial cells connect the entire circulation [system], 60,000 miles worth of blood vessels throughout our body," says Li. "Is this one way that Covid-19 can impact the brain, the heart, the Covid toe? Does SARS-CoV-2 traffic itself through the endothelial cells or get into the bloodstream this way? We don't know the answer to that."

> In another paper that looked at nearly 9,000 people with Covid-19, Mehra showed that the use of statins and ACE inhibitors were linked to higher rates of survival.

If Covid-19 is a vascular disease, the best antiviral therapy might not be antiviral therapy

An alternative theory is that the blood clotting and symptoms in other organs are caused by inflammation in the body due to an over-reactive immune response — the so-called cytokine storm. This inflammatory reaction can occur in other respiratory illnesses and severe cases of pneumonia, which is why the initial reports of blood clots, heart complications, and neurological symptoms didn't sound the alarm bells. However, the magnitude of the problems seen with Covid-19 appear to go beyond the inflammation experienced in other respiratory infections.

"There is some increased propensity, we think, of clotting happening with these [other] viruses. I think inflammation in general promotes that," Sethi says. "Is this over and above or unique for SARS-CoV-2, or is that just because [the infection] is just that much more severe? I think those are all really good questions that unfortunately we don't have the answer to yet."

Anecdotally, Sethi says the number of requests he received as the director of the pulmonary embolism response team, which deals with blood clots in the lungs, in April 2020 was two to three times the number in April 2019. The question he's now trying to answer is whether that's because there were simply more patients at the hospital during that month, the peak of the pandemic, or if Covid-19 patients really do have a higher risk for blood clots.

"I suspect from what we see and what our preliminary data show is that this virus has an additional risk factor for blood clots, but I can't prove that yet," Sethi says.

The good news is that if Covid-19 is a vascular disease, there are existing drugs that can help protect against endothelial cell damage. In another *New England Journal of Medicine* paper that looked at nearly 9,000 people with Covid-19, Mehra showed that the use of statins and ACE inhibitors were linked to higher rates of survival. Statins reduce the risk of heart attacks not only by lowering cholesterol or preventing plaque, they also stabilize existing plaque, meaning they're less likely to rupture if someone is on the drugs.

How to Help Your Body and Immune System Recover From Covid-19

It can take a while to feel like yourself again. Here's how to encourage healing.

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"It turns out that both statins and ACE inhibitors are extremely protective on vascular dysfunction," Mehra says. "Most of their benefit in the continuum of cardiovascular illness — be it high blood pressure, be it stroke, be it heart attack, be it arrhythmia, be it heart failure — in any situation the mechanism by which they protect the cardiovascular system starts with their ability to stabilize the endothelial cells."

Mehra continues, "What we're saying is that maybe the best antiviral therapy is not actually an antiviral therapy. The best therapy might actually be a drug that stabilizes the vascular endothelial. We're building a drastically different concept."

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