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Hematological features of persons with COVID-19

Qiubai Li [1] · Yulin Cao[1] · Lei Chen[1] · Di Wu[1] · Jianming Yu[1] · Hongxiang Wang[2] · Wenjuan He[1] · Li Chen[2] ·
Fang Dong[3] · Weiqun Chen[4] · Wenlan Chen[1] · Lei Li[5] · Qijie Ran[6] · Qiaomei Liu[7] · Wenxiang Ren[1] · Fei Gao[1] ·
Zhichao Chen[1] · Robert Peter Gale[8] · Yu Hu [1]

Abstract

We studied admission and dynamic demographic, hematological and biochemical co-variates in 1449 hospitalized subjects with coronavirus infectious disease-2019 (COVID-19) in five hospitals in Wuhan, Hubei province, China. We identified two admission co-variates: age (Odds Ratio [OR] = 1.18, 95% Confidence Interval [CI] [1.02, 1.36]; $P = 0.026$) and baseline D-dimer (OR = 3.18 [1.48, 6.82]; $P = 0.003$) correlated with an increased risk of death in persons with COVID-19. We also found dynamic changes in four co-variates, Δ fibrinogen (OR = 6.45 [1.31, 31.69]; $P = 0.022$), Δ platelets (OR = 0.95 [0.90–0.99]; $P = 0.029$), Δ C-reactive protein (CRP) (OR = 1.09 [1.01, 1.18]; $P = 0.037$), and Δ lactate dehydrogenase (LDH) (OR = 1.03 [1.01, 1.06]; $P = 0.007$) correlated with an increased risk of death. The potential risk factors of old age, high baseline D-dimer, and dynamic co-variates of fibrinogen, platelets, CRP, and LDH could help clinicians to identify and treat subjects with poor prognosis.

Introduction

Most people with coronavirus infectious disease-2019 (COVID-19) have mild to moderate symptoms and recover after the appropriate medical intervention(s). However, 15–32 percent develop severe or critical COVID-19 with a case-fatality rate of 1–15% [1–6]. There are few

data of hematological abnormalities in persons with COVID-19 [7–13]. We studied hematological co-variates in 1449 hospitalized persons with COVID-19 in five hospitals in Wuhan, China, interrogating correlations of admission parameters with COVID-19 outcomes.

Methods

Study design and subjects

We studied subjects in seven centers of five hospitals of Union Hospital (Central Hospital, Union West Hospital, and Union Tumor Hospital), Wuhan Central Hospital,

These authors contribution equally: Qiubai Li, Yulin Cao, Lei Chen, Di Wu, Jianming Yu, Hongxiang Wang, Wenjuan He, Li Chen, Fang Dong, Weiqun Chen

✉ Qiubai Li
qiubaili@hust.edu.cn

✉ Zhichao Chen
chenzhichao@hust.edu.cn

✉ Yu Hu
dr_huyu@126.com

1 Institute of Hematology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, 430022 Wuhan, China

2 Department of Hematology, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

3 Intensive Care Units of Wuhan Third Hospital, Tongren Hospital of Wuhan University, Wuhan, China

4 Key Laboratory for Molecular Diagnosis of Hubei Province, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

5 Wuhan Jin-Yin-Tan Hospital, Wuhan, China

6 Department of Hematology, General Hospital of Central Theater Command, PLA, 300700 Wuhan, China

7 Medical Records Statistics Department of Wuhan Third Hospital, Tongren Hospital of Wuhan University, Wuhan, China

8 Center for Hematology Research, Department of Immunology and Inflammation, Imperial College London, London, UK

General Hospital of Central Theater Command, PLA, Wuhan Third Hospital, and Wuhan Jin-Yin-Tan Hospital between January 20, and April 4, 2020. Subjects were studied on admission for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-infection by quantitative real-time reverse transcriptase-polymerase chain reaction (qRT-PCR) of nasal and pharyngeal swabs and/or blood test for anti-SARS-CoV-2 IgG/IgM antibodies using a colloidal-gold-based 2019-nCoV IgG/IgM Detection Kit (Nanjing Vazyme Medical Technology, Nanjing, China). COVID-19 was diagnosed according to World Health Organization interim guidance and the Novel Coronavirus Pneumonia Diagnosis and Treatment Program of the National Health Commission of China [14, 15]. Severity of COVID-19 was graded as follows: (1) mild; mild clinical symptoms, no pneumonia on lung CT; (2) common: fever, cough and lung CT with pneumonia; (3) severe: respiratory distress (respiratory rate > 30 min^{-1}, oxygen saturation (O_{2Sat}) ≤ 93 percent at rest and/or ratio of arterial oxygen partial pressure to fractional inspired oxygen ≤300 mmHg (P_{aO2}/F_{IO2}); and (4) critical: aforementioned criteria of respiratory failure receiving mechanical ventilation, shock, and/or organ failure other than lung and/or intensive care unit (ICU) hospitalization [12, 15]. Subjects were treated as described below or according to Chinese government guidelines [15–18]. The study was approved by the Ethics Committees of Union Hospital (2020-0095) and of Wuhan Central Hospital (2020-007). Written and oral informed consent from subjects was waived by the Ethics Committees.

Data collection

Electronic medical records of subjects including epidemiological, demographic, and laboratory data. Outcomes included: (1) death; (2) alive with two successive negative SARS-Cov-2 qRT-PCR tests; (3) interval from symptoms to hospital admission, discharge, or death; (4) negative qRT-PCT test; and (5) interval from admission to COVID-19 progression. Data collection forms were reviewed and verified independently by two researchers. A third researcher adjudicated discordances.

Statistical analysis

Categorical variables were described as frequency rates and percentages and continuous variables by median and inter-quartile range (IQR). Significance was tested by Kruskal–Wallis test or the Fisher exact test. A two-sided $P <$ 0.05 was considered significant. Locally weighted regression and smoothing scatterplot was performed to equate a smooth curve about the relationship between time and values of laboratory parameters. Uni- and multivariable logistic regression models were used to interrogate co-variates associated

with in-hospital death. Analyses were not been adjusted for multiple comparisons. Data were analyzed as of April 4, 2020.

Results

Baseline co-variates corelated with death from COVID-19

We analyzed data from 3559 consecutive subjects. One thousand seven hundred were excluded because of missing data of SARS-CoV-2 qRT-PCR or anti-SARS-CoV-2 IgG/IgM, 410 with co-morbidities and/or receiving drugs that would potentially affect bone marrow function (Supplementary Fig. 1). The resulting study cohort was 1449 subjects.

Seven hundred and thirty-three subjects (51%) were male. Median age was 57 years (IQR, 42–66 years), 576 (40%) were 60–79 years and 66 (5%), ≥80 years. Common signs and symptoms on admission included dry (485; 43%) or productive cough (551; 38%), fatigue (531; 37%), and shortness of breath (520; 37%). Eighty three subjects (6%) were smokers and 71 (6%), health care providers. Four subjects were exposed in the Hunan Wholesale Seafood Market and 94 (6%), close contact with persons with SARS-CoV-2-infection. Twenty nine subjects (2%) had mild COVID-19, 956 (66%), moderate, 347 (24%), severe and 117 (8%), critical. Lung computed tomography (CT) scan showed bilateral pneumonia in 1215 (87%), ground-glass opacity in 1041 (75%), patchy shadows in 579 (42%), and consolidation in 242 (18%). Eight hundred and twenty-six (57%) subjects had ≥1 abnormal liver function tests. One hundred and forty-four (10%), acute respiratory distress syndrome (ARDS) and 392 (27%), bacterial co-infections. Other complications had <10% frequencies including heart, acute kidney abnormalities, septic shock, and multiple organ failure. One hundred and fifty-six subjects (14%) received high-flow nasal cannula oxygen, 98 (7%), non-invasive ventilation (no intubation), 54 (4%), invasive ventilation (intubation), and four extracorporeal membrane oxygenation (ECMO). Median ICU stay was 12 days (IQR, 5–21 days). Median intervals from symptom onset to a negative SARS-CoV-2 qRT-PCR RNA, progression and death or discharge were 22 days (IQR 17–28 days), 10 days (IQR 7–14 days), and 30 days (IQR 23–37 days).

At the time of data lock 1327 (92%) subjects were alive and discharged; 122 (8%), died (Table 1). Subjects who died were significantly older than survivors (median 69 versus 55 years; $P < 0.001$) and more likely male (74% versus 48%; $P <$ 0.001), with more frequent fatigue (54% versus 35%; $P <$ 0.001), chills (26% versus 15%; $P < 0.001$), productive cough (50% versus 37%, $P = 0.006$), shortness of breath (66% versus 35%; $P < 0.001$), a higher temperature on admission

Table 1 Baseline characteristics of survivors and non-survivors with COVID-19.

	Total $n = 1449$	Alive $n = 1327$	Died $n = 122$	P value
Characteristics				
Age, median (IQR), years	57 (42, 66)	55 (41, 65)	69 (63, 78)	<0.001
Age distribution				
<40 years	306 (21)	305 (23)	1 (0.8)	
40–59 years	501 (35)	481 (36)	20 (16)	
60–79 years	576 (40)	499 (38)	77 (63)	
≥80 years	66 (5)	42 (3)	24 (20)	
Female sex	716 (49)	684 (52)	32 (26)	<0.001
Smoking history	83 (6)	66 (5)	17 (15)	<0.001
Health care provider	71 (6)	69 (7)	2 (2)	0.038
Exposure history				0.026
Huanan Seafood Market	4 (0.28)	2 (0.15)	2 (2)	
Close contact with patients	94 (6)	89 (7)	5 (4)	
Signs and symptoms				
Temperature (°C)	36.7 (36.4, 37.1)	36.6 (36.4, 37.0)	36.8 (36.5, 37.8)	<0.001
Shortness of breath	520 (37)	456 (35)	64 (66)	<0.001
Dry cough	485 (43)	437 (43)	48 (44)	0.824
Wet cough	551 (38)	491 (37)	60 (50)	0.006
Fatigue	531 (37)	466 (35)	65 (54)	<0.001
Nausea or vomiting	88 (6)	83 (6)	5 (4)	0.43
Diarrhea	186 (13)	170 (13)	16 (13)	0.897
Chill	226 (16)	194 (15)	32 (26)	<0.001
Runny nose	30 (2)	28 (2)	2 (1.6)	0.999
Myalgia	255 (18)	231 (17)	24 (20)	0.502
Headache	89 (6)	84 (6)	5 (4)	0.43
Staging				<0.001
Mild	29 (2)	29 (2)	0 (0)	
Moderate	956 (66)	951 (72)	5 (4)	
Severe	347 (24)	332 (25)	15 (12)	
Critical	117 (8)	15 (1)	102 (84)	
Imaging features				
Bilateral pneumonia	1215 (87)	1117 (86)	98 (95)	0.01
Consolidation	242 (18)	207 (16)	35 (35)	<0.001
Ground-glass opacity	1041 (75)	974 (76)	67 (67)	0.059
Patchy shadows	579 (42)	532 (41)	47 (47)	0.218
Complications				
ARDS	144 (10)	37 (3)	107 (88)	<0.001
Bacterial infections	392 (27)	288 (22)	104 (85)	<0.001
Septic shock	45 (4)	1 (0.1)	44 (40)	<0.001
Acute kidney injury	49 (3)	7 (0.5)	42 (34)	<0.001
Cardiac injury	125 (9)	58 (4)	67 (55)	<0.001
Liver damage	826 (57)	721 (54)	105 (86)	<0.001
Gastrointestinal bleeding	20 (1)	4 (0.3)	16 (13)	<0.001
Coagulopathy	28 (2)	0 (0)	28 (23)	<0.001
Multiple organ failure	72 (5)	3 (0.2)	69 (57)	<0.001

Table 1 (continued)

	Total $n = 1449$	Alive $n = 1327$	Died $n = 122$	*P* value
Treatments				
Antibiotics	1203 (85)	1084 (83)	119 (98)	<0.001
Antimycotics	44 (3)	17 (1)	27 (22)	<0.001
Oseltamivir	604 (42)	564 (43)	40 (33)	0.037
Umifenovir	1099 (76)	1004 (76)	95 (78)	0.688
Lopinavir and Ritonavir	276 (24)	232 (23)	44 (40)	<0.001
Interferon	297 (21)	269 (20)	28 (23)	0.483
Corticosteroids	576 (40)	471 (35)	105 (86)	<0.001
Intravenous immunoglobin	381 (28)	314 (25)	67 (55)	<0.001
High-flow nasal cannula oxygen therapy	156 (14)	59 (6)	97 (88)	<0.001
Noninvasive mechanical ventilation	98 (7)	21 (2)	77 (63)	<0.001
Invasive mechanical ventilation	54 (4)	7 (0.5)	47 (39)	<0.001
ECMO	4 (0.4)	1 (0.1)	3 (3)	0.003
Outcomes				
ICU admission	63 (4)	23 (2)	40 (33)	<0.001
Time from illness onset to ICU admission, median (IQR), days	14 (10, 19)	10 (8, 18)	15 (12, 20)	0.141
ICU length of stay, median (IQR), days	12 (5, 21)	11 (8, 21)	12 (4, 21)	0.619
Time from illness onset to repeated negatively tests of SARS-CoV-2, median (IQR), days	22 (17, 28)	22 (17, 28)	19 (12, 26)	0.066
Time from illness onset to admission, median (IQR), days	10 (7, 15)	10 (7, 16)	10 (7, 12)	0.017
Time from illness onset to progression, median (IQR), days	10 (7, 14)	10 (6, 14)	12 (9, 19)	0.001
Time from illness onset to outcome, median (IQR), days	30 (23, 37)	30 (24, 38)	21 (15, 29)	<0.001
Time from diagnosis to outcome, median (IQR), days	19 (13, 27)	20 (13, 27)	11 (5, 17)	<0.001
Time from admission to outcome, median (IQR), days	18 (13, 23)	18 (13, 23)	11 (6, 20)	<0.001

IQR interquartile ranges, *ARDS* acute respiratory distress syndrome, *ECMO* extracorporeal membrane oxygenation, *ICU* intensive care unit, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2.

(median 36.8 °C; IQR 36.5–37.8 °C versus median 36.6 °C; IQR 36.4–37.0 °C; *P* < 0.001), bilateral pneumonia (95% versus 86%; *P* = 0.01), and/or consolidation (35% versus 16%, *P* < 0.001) on lung CT scan but similar dry cough (44% versus 43%, *P* = 0.824), diarrhea (both 13%; *P* = 0.897), and myalgia (20% versus 17%; *P* = 0.502).

Median interval from symptom(s) onset to admission was 10 days in survivors (IQR 7–16 days) versus 10 days (IQR 7–12 days; *P* = 0.017) in non-survivors. Median interval from admission to progression in survivors was briefer (10 days [IQR 6–14 days] versus 12 days [IQR 9–19; *P* = 0.001). Median interval from onset to ICU admission was 14 days (IQR 10–19 days) and median ICU stay, 12 days (IQR 5–21 days) with no significate difference between survivors and non-survivors (*P* = 0.141 and *P* =

0.619). Subjects who died were more likely to have complications (122 [100%] versus 741 [56%]; *P* < 0.001) including acute respiratory distress syndrome (ARDS; 107 [88%] versus 37 [3%]; *P* < 0.001), liver function test abnormalities (105 [86%] versus 721 [54%]; *P* < 0.001) and bacterial infections (104 [85%] versus 288 [22%]; *P* < 0.001). More subjects dying received high-flow nasal cannula oxygen therapy (97 [88%] versus 59 [6%]; *P* < 0.001). Four subjects received ECMO including one survivor.

Blood hematological co-variates of survivors and non-survivors

We first compared admission hematological co-variates between survivors and non-survivors. Subjects who died had a higher

Table 2 Blood hematological co-variates of survivors and non-survivors with COVID-19.

	N	Total	Alive	Died	P value
Hemoglobin, g/L (115–150)					
Baseline	1437	129 (119–139)	128 (119–139)	131 (122–143)	0.068
Max	1101	132 (122–142)	131 (126–146)	136 (122–142)	0.049
Min	1101	119 (108–131)	120 (110–131)	105 (78–126)	<0.001
White blood cell, ×10E + 9/L (3.5–10)					
Baseline	1420	5 (4–7)	5 (4–7)	8 (6–11)	<0.001
Max	1421	7 (5–9)	7 (5–8)	16 (12–21)	<0.001
Min	1421	5 (4–6)	5 (4–6)	6 (4–9)	<0.001
Neutrophil, ×10E + 9/L (1.8–6.3)					
Baseline	1417	3 (2–5)	3 (2–4)	7 (5–10)	<0.001
Max	1421	5 (3–7)	4 (3–6)	14 (11–20)	<0.001
Min	1421	3 (2–4)	3 (2–4)	5 (3–8)	<0.001
Lymphocyte, ×10E + 9/L (1.1–3.2)					
Baseline	1440	1.2 (0.8–1.6)	1.2 (0.9–1.7)	0.5 (0.4–0.8)	<0.001
Min	1411	1.0 (0.7–1.4)	1.1 (0.8–1.5)	0.3 (0.2–0.5)	<0.001
Monocyte, ×10E + 9/L (0.1–0.6)					
Baseline	1408	0.4 (0.3–0.53)	0.4 (0.3–0.5)	0.3 (0.2–0.5)	<0.001
Max	1419	0.5 (0.4–0.7)	0.5 (0.4–0.7)	0.5 (0.4–0.8)	0.305
Min	1419	0.3 (0.2–0.4)	0.3 (0.3–0.4)	0.2 (0.1–0.3)	<0.001
Platelet, ×10^9 E + 9/L (125–350)					
Baseline	1415	206 (159–264)	208 (164–268)	166 (109–223)	<0.001
Max	1420	258 (204–325)	263 (208–331)	190 (134–255)	<0.001
Min	1420	176 (135–224)	180 (143–226)	80 (39–147)	<0.001

Data are presented as medians (interquartile ranges, IQR). p values were calculated by Mann–Whitney U test, χ^2 test, or Fisher's exact test, as appropriate.

median WBC (8 × 10E + 9/L [IQR 6–11 × 10E + 9/L] versus 5 × 10E + 9/L [IQR 4–7 × 10E + 9/L]; $P < 0.001$), higher median neutrophils (7 × 10E + 9/L [IQR 5–10 × 10E + 9/L] versus 3 × 10E + 9/L [IQR 2–4 ×10E + 9/L]; $P < 0.001$), lower median lymphocytes (0.5 × 10E + 9/L [IQR 0.4–0.8 × 10E + 9/L] versus 1.2 × 10E + 9/L [IQR 0.9–1.7 × 10E + 9/L]; $P < 0.001$) and lower median platelets (166 × 10E + 9/L [IQR 109–223 × 10E + 9/L] versus 208 × 10E + 9/L [IQR 164–268 × 10E + 9/L]; $P < 0.001$) compared with survivors (Table 2).

Blood lymphocyte subsets

We next analyzed baseline blood lymphocyte subsets between subjects who died and survivors (Table 3). Subjects who died had lower median CD3-positive cells (140 × 10E + 9/L [IQR 75–190 × 10E + 9/L] versus 381 × 10E + 9/L [IQR 2–918 × 10E + 9/L]; $P = 0.023$), CD3-positive/CD4-positive cells (71 × 10E + 9/L [IQR 46–107 × 10E + 9/L] versus 227 × 10E + 9/L [IQR 1–487 × 10E + 9/L]; $P = 0.036$), CD3-positive/CD8-positive cells (49 × 10E + 9/L [IQR 14–64 × 10E + 9/L] versus 141 × 10E + 9/L [IQR, 1–308 × 10E + 9/L]; $P = 0.023$) and lower median proportions of CD3-positive cells (59% [IQR 50–67%] versus 72% [IQR 63–78%]; $P < 0.001$), median proportions of CD3-positive/CD8-positive cells (14% [IQR 10–18%] versus 24% [IQR 19–30%]; $P < 0.001$) and median

proportions of B cells (16% [IQR 10–28%] versus 12% [IQR 9–17%]; $P = 0.022$). There were no significant differences in median proportions of CD3-positive/CD4-positive T- or natural-killer (NK)-cells, nor in concentrations of B cells or NK-cells between survivors and non-survivors.

Clotting co-variates

Baseline and maximum values of prothrombin time, activated partial thromboplastin time, and D-dimer concentrations were significantly higher in subjects who died compared with survivors. In contrast, fibrinogen concentration was higher at baseline in subject who died (median 4.3 g/L [IQR, 3.2–5.2 g/L] versus 3.6 g/L [IQR 2.9–4.5 g/L]; $P < 0.001$) but had lower minimum values (2.6 g/L [IQR 1.7–3.9 g/L] versus 3.2 g/L [IQR 2.6–3.9 g/L]; $P < 0.001$; Table 4).

Inflammatory and biochemical co-variates

Median admission concentrations of C-reactive protein (CRP) (93 mg/L [IQR 58–125 mg/L] versus 9 mg/L [IQR 3–30 mg/L]; $P < 0.001$), procalcitonin (0.2 ng/ml [IQR 0.12–0.6 ng/ml] versus 0.05 ng/ml [IQR 0.04–0.1 ng/ml]; $P < 0.001$) and lactate dehydrogenase (LDH) (470 U/L [IQR 359–599 U/L] versus 199 U/L [IQR 161–258 U/L]; $P < 0.001$) were significantly higher in subjects who died

Table 3 The lymphocyte subsets of peripheral blood in of survivors and non-survivors with COVID-19.

Lymphocyte subset	N	Total	Alive	Died	P value
CD3+ (%)	579	72 (62–78)	72 (63–78)	59 (50–67)	<0.001
CD3 concentration × 10E + 9/L	246	359 (2–901)	381 (2–918)	140 (75–190)	0.023
CD3+CD4+ (%)	579	41 (33–48)	41 (33–48)	37 (28–48)	0.443
CD3+CD4+ concentration × 10E + 9/L	246	200 (1–481)	227 (1–487)	71 (46–107)	0.036
CD3+CD8+ (%)	579	23 (18–30)	24 (19–30)	14 (10–18)	<0.001
CD3+CD8+ concentration × 10E + 9/L	246	119 (1–302)	141 (1–308)	49 (14–64)	0.023
NK cell (%)	415	10 (6–17)	10 (6–17)	10 (5–12)	0.29
NK cell concentration × 10E + 9/L	246	76 (0.4–185)	77 (0.4–188)	41 (19–102)	0.453
B lymphocyte (%)	415	13 (9–18)	12 (9–17)	16 (10–28)	0.022
B lymphocyte concentration × 10E + 9/L	246	96 (0.3–178)	98 (0.3–188)	55 (22–91)	0.136
CD4+/CD8+ ratio					
Max	577	2 (1.4–2.6)	1.9 (1.4–2.6)	3.0 (1.9–4.5)	<0.001
Min	489	1.6 (1.2–2)	1.57 (1.2–2)	1.6 (1.3–2.3)	0.336

Data are median (IQR), n (%), or n/N (%). Cell count at presentation (cells/ul). p values were calculated by Mann–Whitney U test, χ^2 test, or Fisher's exact test, as appropriate.

NK cell natural killer cell

Table 4 Clotting factor levels of survivors and non-survivors with COVID-19.

	N	Total	Alive	Died	P value
PT, s (11–16)					
Baseline	1055	13 (12–13)	13 (12–13)	14 (13–15)	<0.001
Max	1035	13 (12–14)	13 (12–14)	17 (14–20)	<0.001
APTT, s (28–43.5)					
Baseline	1055	34 (30–38)	34 (30–37)	35 (300–40)	0.019
Max	1289	34 (30–38)	34 (30–37)	40 (34–50)	<0.001
D-dimer, mg/L (<0.5)					
Baseline	1239	0.4 (0.2–0.9)	0.4 (0.2–0.8)	3.6 (0.9–8)	<0.001
Max	1262	0.6 (0.2–1.6)	0.5 (0.2–1)	8 (6–8)	<0.001
Fibrinogen, g/L (2–4)					
Baseline	1304	3.7 (2.9–4.6)	3.6 (2.9–4.5)	4.3 (3.2–5.2)	<0.001
Min	976	3.2 (2.5–3.9)	3.2 (2.6–3.9)	2.6 (1.7–3.9)	<0.001

PT prothrombin time, APTT activated partial thromboplastin time.

compared with survivors (Table 5). Subjects who died were more likely to have abnormal heart, liver, and/or kidney function and to have higher admission median concentrations of interleukin-6 (IL-6; 71 pg/ml [IQR 29–442 pg/ml] versus 9 pg/ml [IQR 4–30 pg/ml]; $P < 0.001$) and interleukin-10 (IL-10; 11 pg/ml IQR [6–30 pg/ml] versus 4 pg/ml [IQR 3–5 pg/ml]; $P < 0.001$). There were no significant differences in concentrations of interleukins-2 (IL-2) or -4 (IL-4), tumor necrosis factor (TNF)-α, or interferon (IFN)-γ between survivors and non-survivors.

Dynamic changes in hematological co-variate

Next, we studied dynamic changes in hematological co-variates between survivors and non-survivors in 390 subjects from Wuhan Third Hospital with daily determinations

(Supplementary Table 1). Subjects who died had higher concentrations of WBCs, neutrophils, D-dimmer, PT, LDH, and CRP but lower concentrations of lymphocytes and platelets throughout their hospitalization. These dynamic changes are displayed in Fig. 1.

Uni- and multivariable analyses

We analyzed admission hematological co-variates and their multiple measurements considering changes (Δ = Max − Min, Max − baseline, or baseline − Min) correlated with risk of death in all subjects (Supplementary Table 2). In a multivariable logistic regression model, age (Odds Ratio [OR] = 1.18 [1.02, 1.36]; $P = 0.026$), baseline D-dimer (OR = 3.18 [1.48, 6.82]; $P = 0.003$), Δ fibrinogen (OR = 6.45 [1.31, 31.69]; $P = 0.022$), Δ platelets (OR = 0.95

Table 5 Biochemical parameters and inflammatory cytokines of survivors and non-survivors with COVID-19.

	N	Total	Alive	Died	P value
CRP, mg/L (<8)					
Baseline	1046	11 (3, 44)	9 (3, 30)	93 (58, 125)	<0.001
Max	1063	14 (4, 55)	11 (3, 38)	140 (110, 181)	<0.001
Procalcitonin, ng/ml (<0.5)					
Baseline	1273	0.05 (0.05, 0.1)	0.05 (0.04, 0.1)	0.2 (0.12, 0.6)	<0.001
Max	1065	0.07 (0.04, 0.1)	0.06 (0.04, 0.1)	1.2 (0.4, 4)	<0.001
LDH, U/L (109–245)					
Baseline	1338	207 (165, 283)	199 (161, 258)	470 (359, 599)	<0.001
Max	1354	215 (174, 302)	207 (169, 271)	707 (509, 1154)	<0.001
Ferritin, ng/ml (4.6–204)	231	542 (226, 1207)	446 (191, 906)	1584 (1196, 2000)	<0.001
ALT, U/L (5–35)	1429	39 (22, 68)	37 (21, 66)	62 (34, 150)	<0.001
AST, U/L (8–40)	1428	31 (22, 49)	30 (22, 44)	68 (45, 143)	<0.001
Total bilirubin, μmol/L (5.1–19)	1245	14 (10, 19)	13 (10, 17)	25 (16, 39)	<0.001
Creatine kinase, U/L (26–140)	1151	87 (54, 150)	81 (52, 130)	253 (104, 656)	<0.001
BNP, pg/ml (<100)	627	50 (14, 160)	39 (12, 115)	454 (116, 1377)	<0.001
Myoglobin, ng/ml (<140)	718	32 (21, 60)	29 (21, 49)	476 (147, 1200)	<0.001
Troponin I, ng/L (<26.2)	830	3 (1, 10)	2 (0.9, 7)	212 (48, 1011)	<0.001
BUN, mmol/L (2.9–8.2)	1414	5 (4, 6)	5 (4, 6)	14 (8, 23)	<0.001
Scr, μmol/L (44–106)	1414	70 (59, 83)	69 (59, 81)	100 (71, 211)	<0.001
IL-2, pg/ml (0.1–4.1)	344	3 (3, 4)	3 (3, 4)	3 (3, 5)	0.849
IL-4, pg/ml (0.1–3.2)	380	3 (2, 4)	3 (2, 4)	2 (2, 4)	0.804
IL-6, pg/ml (0.1–2.9)	659	10 (4, 37)	9 (4, 30)	71 (29, 442)	<0.001
IL-10, pg/ml (0.1–5)	380	4 (3, 6)	4 (3, 5)	11 (6, 30)	<0.001
TNF α, pg/ml (0.1–23)	380	3 (2, 6)	4 (2, 6)	3 (2, 4)	0.183
IFN γ, pg/ml (0.1–18)	380	3 (2, 4)	3 (2, 4)	3 (2, 4)	0.88

CRP C-reactive protein, *LDH* lactate dehydrogenase, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *BNP* brain natriuretic peptide, *BUN* blood urea nitrogen, *Scr* serum creatinine, *IL* interleukin, *TNF* tumor necrosis factor, *IFN* interferon.

[0.90–0.99]; $P = 0.029$), Δ CRP (OR = 1.09 [1.01, 1.18]; $P = 0.037$) and Δ LDH (OR = 1.03 [1.01, 1.06]; $P = 0.007$) correlated with an increased risk of death (Table 6).

Discussion

Our data indicate two baseline co-variates (age and D-dimer) on admission and four dynamic co-variates (Δs of concentrations of CRP, LDH, fibrinogen, and platelets) correlate with an increased risk of death in almost 1500 hospitalized persons with COVID-19. In our dataset, we could not confirm other co-variates such as male sex [19], and comorbidities of atherosclerotic cardiovascular disease [20] and hypertension [21] that had been excluded from the present study.

Two admission co-variates correlated with risk of death: age and D-dimer concentration. Similar correlates are reported by others in COVID-19 [8, 19, 20, 22–24] and in two other coronavirus infections, severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome [25, 26]. Age related immune deficiency may be the explanation of this association but is unproved [27]. High D-dimer concentration may result from the inflammation associated with COVID-19 and subsequent activation of coagulation [28]. Several potential risk factors during hospitalization, including disseminated intravascular coagulation, infection, dehydration, prolonged immobilization, mechanical ventilation, and central venous catheter use may further increase D-dimer concentrations [29, 30].

Four dynamic co-variates correlated with an increased risk of death including Δs of concentrations of CRP, LDH, fibrinogen, and platelets. Similar data are rarely reported in COVID-19-infection [7, 8, 31]. Higher admission LDH concentration was reported to be a risk factor for death by different studies [19, 23, 32]. However, we found the dynamics were more predictive. Han et al.
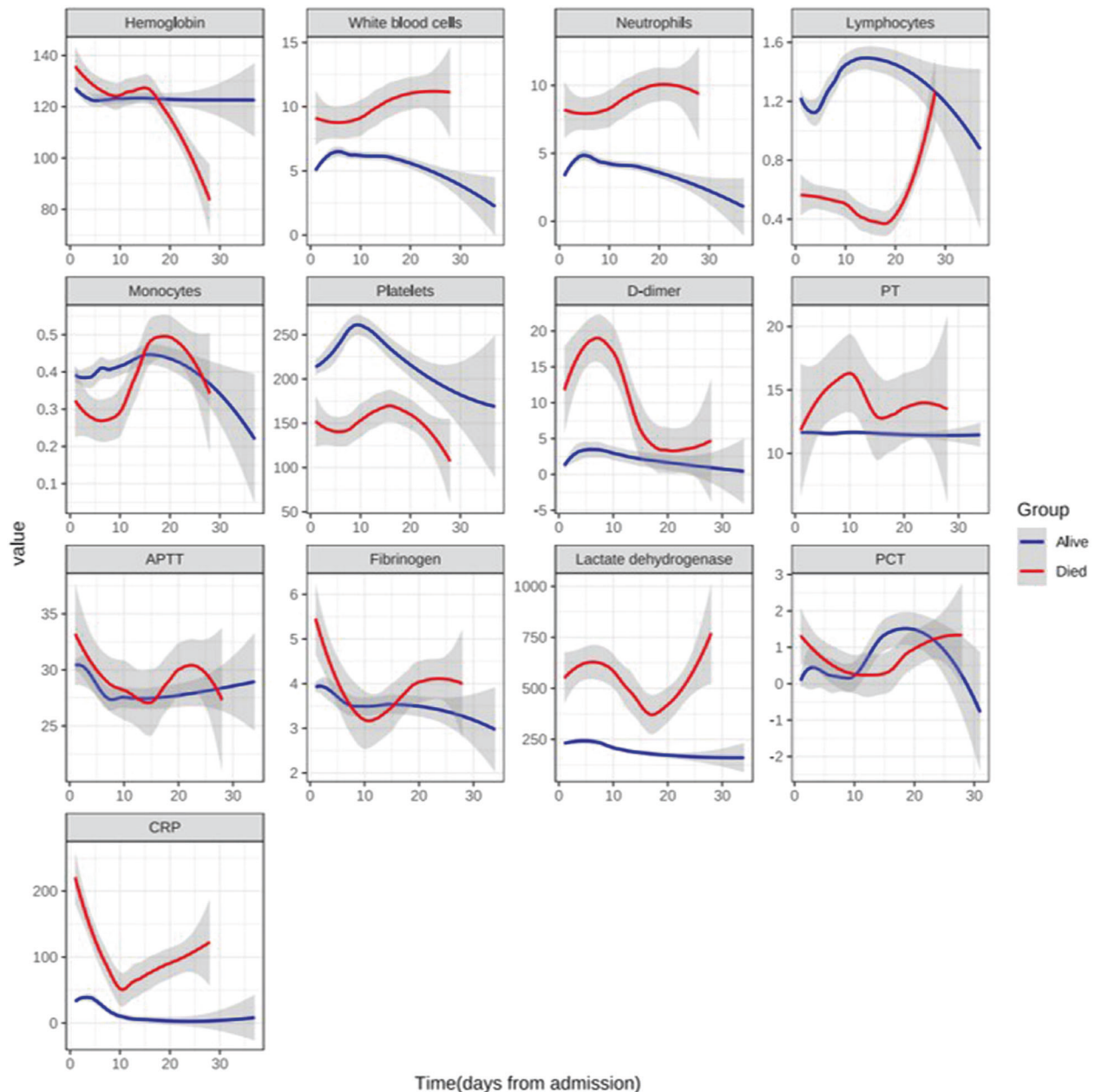
Fig. 1 Dynamic changes of hematological variables in patients with COVID-19 during hospitalization. The *Y*-axis "value" include units of all above data: ×10E + 9/L for white bloods cells, neutrophils, lymphocytes, monocytes, and platelets; g/L for hemoglobin, fibrinogen (FIB); mg/L for D-dimer; s for prothrombin time (PT), activated partial thromboplastin time (APTT); U/L for lactate dehydrogenase (LDH); ng/ml for procalcitonin (PCT); mg/L for C-reactive protein (CRP). Data are presented as medians (interquartile ranges, IQR).

report a dynamic decrease of CRP concentration in 17 subjects with COVID-19 who recovered [31]. There are few data on dynamics of fibrinogen concentration in persons with COVID-19. Tang et al. reported differences in dynamic fibrinogen between survivor and non-survivors, but this dynamic co-variate was not identified to be a risk factor for death [7]. Admission and dynamic platelets are not reported to correlate with risk of death in persons with COVID-19 [22, 33, 34].

Our study has important limitations. It was retrospective and researchers were not blinded to the outcome when they analyzed the data. Also, we have no external validation cohort. Finally, we did not adjust for multiple comparisons. As such, our conclusions should be interpreted as exploratory and descriptive. Because subjects more likely to die have profound changes in several of these co-variates the correlations we report should not be assumed to be *cause-and-effect*.

Table 6 Multivariate analysis of hematological co-variates associated with in-hospital death of patients with COVID-19.

	Odds Ratio	95% Confidence Interval	*P* value
Age (years)	1.18	(1.02–1.36)	0.026
Baseline D-dimer (mg/L)	3.18	(1.48–6.82)	0.003
Δ Platelet (×10E + 9/L)[a]	0.95	(0.90–0.99)	0.029
Δ Neutrophil (×10E + 9/L)[a]	1.31	(0.99–1.72)	0.058
Δ Fibrinogen (g/L)[b]	6.45	(1.31–31.69)	0.022
Δ C-reactive protein (mg/L)[c]	1.09	(1.01–1.18)	0.037
Δ Lactate dehydrogenase (U/L)[c]	1.03	(1.01–1.06)	0.007

[a]Δ = Max − Min.

[b]Δ = baseline − Min.

[c]Δ = Max − baseline.

In conclusion, we show admission hematological co-variates except D-dimer concentration are not associated with an increased risk of death in a large cohort of subjects with COVID-19. However, dynamic measurements of platelets, fibrinogen, CRP, and LDH correlate with risk of death. We await validation of our conclusions.

Data availability

All data generated or analyzed during this study are included in this published article and its Supplementary Information files.

Compliance with ethical standards

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