Clinical Characteristics and Risk Factors of Disseminated Intravascular Coagulation in Patients with COVID-19

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Abstract

Background: Coronavirus disease 2019 (COVID-19) has spread globally. However, the association between COVID-19 and disseminated intravascular coagulation (DIC) has been scarcely addressed. We aimed to systematically characterize the clinical features and examine risk factors for DIC development in COVID-19 patients.

Methods: In this single-centered, retrospective, and observational study, all patients with DIC (N=59) and 270 patients without DIC were matched by propensity score matching based on age, sex, and comorbidities. Demographic data, symptoms, radiological, laboratory examinations, and clinical outcomes were compared between patients with and without DIC. Furthermore, univariable and multivariable logistic regression were used to explore the risk factors associated with DIC development in COVID-19 patients.

Results: Higher proportion of patients with DIC and COVID-19 (54 of 59 [91·53%]) developed into death than non DIC patients (58 of 270 [21·48%]). Patients with DIC presented aggravated inflammation responses, liver damage, and especially coagulation dysfunction. Moreover, in addition to previously reported coagulation-related markers, such as FDP, D-dimer, and platelet, we also identified several novel risk factors associated with DIC development, including decreased fibrinogen (OR=0·476, 95%CI=0·380-0·596, *P*<0·0001) and ALB (0·901, 0·845- 0·961, *P*=0·0015), and elevated IL-6 (1·010, 1·005-1·015, *P*=0·00017) and TNF-α (1·053, 1·016-1·091, *P*=0·0045).

Conclusions: Patients with DIC and COVID-19 were predisposed to poor clinical outcomes. These risk factors identified may be helpful for early surveillance of disease progression and making standardized treatment strategies.

Introduction

The coronavirus disease 2019 (COVID-19) which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread all over the world. Up to Sep 6, 2020, there were 26,763,217 confirmed cases and 876,616 deaths, which still affected 216 countries.[1] Furthermore, the COVID-19 pandemic poses a significant threat to human health and the economy. Considering the increased risk of developing severe complications, admission to the intensive care unit (ICU), or even death in patients with COVID-19, early identification and the effective treatments for the patients with common fatal complications are urgently needed.

Notably, initial analyses of patient characteristics from China have shown that organ damage, acute respiratory distress syndrome (ARDS), septic shock, and disseminated intravascular coagulation (DIC) are highly prevalent complications in COVID-19 patients.[2,3] Among the complications, DIC is a serious and fatal disease caused by infection, solid cancers, and trauma,[4] which is also one of the important causes of death in severe patients with COVID-19.[3] Additionally, the ill-critical patients with COVID-19

accompanied with coagulation dysfunction have a high risk of DIC development,[5] which results in microcirculation disorder, multiple organ failure, and even death.[6] Although some case series have been published, the details of clinical features, symptoms, complications, and treatments have not yet been well described and the estimation of risk factors remains debates in COVID-19 patients who develop DIC. Therefore, it urgently needs to make a comprehensive description of the clinical characteristics and a deeper understanding of the risk factors, which might be of great value to dynamically monitor disease progression and make effective treatments.

Here we performed a single-centered, retrospective, and observational study from Tongji Hospital in Wuhan, China, an epicenter of the COVID-19 outbreak. We aimed to systematically describe the clinical features and explore the risk factors associated with the development of DIC in COVID-19 patients.

Methods

Study design and participants

We conducted a single-centered, retrospective, and observational study at Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (HUST), a designated hospital for COVID-19 patients in Wuhan, China. There were 3,256 COVID-19 patients, who were diagnosed with SARS-CoV-2 according to a positive real-time reverse transcription polymerase chain reaction (RT-PCR) assay in a respiratory tract sample and admitted from January 13, 2020, to March 31, 2020. Among these patients, all patients with DIC (N=59) were enrolled, and 270 patients without DIC were statistically matched by propensity score matching at an approximate ratio of 4:1 based on age, sex, and comorbidities. The comorbidities included hypertension, diabetes, coronary heart disease, chronic obstructive pulmonary disease, cerebrovascular disease, hepatitis, pulmonary tuberculosis, and chronic bronchitis. This study was approved by the Ethics Committee of Tongji Hospital, Tongji Medical College, HUST, and granted a waiver of informed consent from study participants.

Data collection

Epidemiological, clinical, radiological, laboratory, and clinical outcomes data of all patients with laboratory-confirmed SARS-CoV-2 were obtained from the electronic medical records of Tongji Hospital. The collection, review, and verification of the data were completed by a trained team of physicians (YZ, QL, and CL). Any uncertain or missing data were checked and clarified through communication with patients and their families or other health care providers. Standardized and detailed information including demographic data, comorbidities, initial symptoms, and chest computed tomographic (CT) were collected on hospital admission. Laboratory indicators including coagulation test, blood routine, immune cell subsets, inflammatory cytokines and biomarkers, blood gas assay, cardiac function test, and liver function test were examined on the first diagnosed date. The treatments, complications, and clinical outcomes were dynamically monitored during the hospitalization.

Definitions

The diagnosis of DIC is based on a scoring system recommended by the international society on thrombosis and hemostasis (ISTH) Subcommittee of the scientific and Standardization Committee (SSC).[7] The scoring system was evaluated by the laboratory indicators including prothrombin time, platelets, fibrinogen, D-dimer, and fibrin degradation products (FDP). The patients with a score of ≥ 5 were diagnosed as DIC.

The SARS-CoV-2 was examined by the real-time RT-PCR assay. Two pairs of primers were amplified and examined, which targeted the open reading frame 1ab (ORF1ab) and the nucleocapsid protein (N). 5'-CCCTGTGGGTTTTACACTTAA-3' (F), 5'-ACGATTGTGCATCAGCTGA-3' (R), and 5'-VIC-CCGTCTGCGGTATGTGGAAAGGTTATGG-BHQ1-3' (Probe) were the corresponding sequences for target 1 (ORF1ab). And those for target 2 (N) were 5'-GGGGAACTTCTCCTGCTAGAAT-3' (F), 5'-CAGACATTTTGCTCTCAAGCTG-3' (R) and 5'-FAM- TTGCTGCTGCTTGACAGATTTAMRA-3' (Probe). This diagnostic standard was set by the National Center for Disease Control and Prevention of China. Depending on the suggestion, use the positive and the negative control group to make each sample in triplicate.

Statistical analysis

Continuous variables were expressed as mean and standard deviation (SD) for normal distribution data, or median and quartile range (IQR) for skew distribution data. Categorical variables were expressed as number (%). For continuous variables, Student's t-test was used for normal distribution data, and Mann-Whitney U non-parameter test was used for skew distribution data. Pearson's χ^2 test or Fisher's exact test were applied for categorical variables. The risk factors associated with the development of DIC were analyzed by univariate and multivariate logistic regression models. The odds ratio (OR) and 95% confidence interval (CI) were estimated, adjusting for age, gender, and comorbidities. A two-sided p-value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS (22.0) and R (3.50).

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Clinical characteristics of COVID-19 patients with DIC and without DIC

59 COVID-19 patients with DIC and 270 COVID-19 patients without DIC were statistically matched based on age, gender, and comorbidities. There were no significant differences in initial symptoms and chest CT images between these two groups. The results are shown in Table 1.

Table 1
Demographic, clinical and radiographic of COVID-19 patients with DIC and without DIC

Indicators	Total	Patients with DIC	Patients without DIC	p value
	N = 329	N = 59	N = 270	
Characteristics				
Age, years	70·00(64·00–76·00)	70·00(66·00–75·50)	69·00(64·00–76·00)	0·45
Sex	..	..	..	..
Male	206(62·61%)	43(72·88%)	163(60·37%)	0·072
Female	123(37·39%)	16(27·12%)	107(39·63%)	..
Comorbidities				
Hypertension	130(39·51%)	27(45·76%)	103(38·15%)	0·28
Diabetes	46(13·98%)	8(13·56%)	38(14·07%)	0·92
Coronary heart disease	32(9·73%)	6(10·17%)	26(9·63%)	0·90
Chronic obstructive pulmonary disease	4(1·22%)	0	4(1·48%)	1·0[a]
Cerebrovascular disease	20(6·08%)	1(1·69%)	19(7·04%)	0·21
Hepatitis	8(2·43%)	3(5·08%)	5(1·85%)	0·32
pulmonary tuberculosis	9(2·74%)	2(3·39%)	7(2·59%)	1·0
Chronic bronchitis	7(2·13%)	1(1·69%)	6(2·22%)	1·0
Initial symptoms	N = 308	N = 53	N = 255	
Fever	230/308 (74·68%)	44/53 (83·02%)	186/255 (72·94%)	0·13
Cough	216/308 (70·13%)	38/53 (71·70%)	178/255 (69·80%)	0·78
Expectoration	151/308 (49·03%)	29/53 (54·72%)	122/255 (47·84%)	0·36
polypnea	158/308 (51·30%)	33/53 (62·26%)	125/255 (49·02%)	0·079
Fatigue	65/308 (21·10%)	10/53 (18·87%)	55/255 (21·57%)	0·66
Chest tightness	47/308 (15·26%)	7/53 (13·21%)	40/255 (15·69%)	0·65

Indicators	Total	Patients with DIC	Patients without DIC	p value
	N = 329	N = 59	N = 270	
Diarrhoea	62/308 (20·13%)	12/53 (22·64%)	50/255 (19·61%)	0·62
Headache	16/308 (5·19%)	3/53 (5·66%)	13/255 (5·10%)	1·0
Myalgia	32/308 (10·39%)	3/53 (5·66%)	29/255 (11·37%)	0·22
Anorexia	26/308 (8·44%)	5/53 (9·43%)	21/255 (8·24%)	0·99
Vertigo	12/308 (3·90%)	3/53 (5·66%)	9/255 (3·53%)	0·73
Chills	25/308 (8·12%)	4/53 (7·55%)	21/255 (8·24%)	1·0
CT findings				
Ground-glass opacity	102/238 (42·86%)	8/14 (57·14%)	94/224 (41·96%)	0·27
Patchy shadows	192/238 (80·67%)	12/14 (85·71%)	180/224 (80·36%)	0·89
Fibrous stripes	89/238 (37·39%)	6/14 (42·86%)	83/224 (37·05%)	0·66
Pleural thickening	68/238 (28·57%)	7/14 (50·00%)	61/224 (27·23%)	0·13
Nodules	18/238 (7·56%)	2/14 (14·29%)	16/224 (7·14%)	0·65
Lymphadenia	78/238 (32·77%)	8/14 (57·14%)	70/224 (31·25%)	0·087
Bilateral pulmonary	230/238 (96·64%)	14/14 (100%)	216/224 (96·43%)	1·0[a]
Right lung	2/238 (0·84%)	0	2/224 (0·89%)	1·0[a]
Left lung	5/238 (2·10%)	0	5/224 (2·23%)	1·0[a]

Abbreviation: COVID-19, Coronavirus disease 2019; CT, Computerized; DIC, Disseminated intravascular coagulation, IQR, Interquartile range.

Continuous variables were described as median (IQR). *P* values were calculated by Mann-Whitney U non-parameter test for skewed distributed data. Categorical variables were expressed as number (%). *P* values were calculated by Pearson's χ^2 test or Fisher's exact test (a). * $P < 0{\cdot}05$.

We observed that patients with DIC had aggravated coagulation dysfunction compared to patients without DIC (Table 2). The level of D-Dimer (11·52 [IQR 1·96 – 21·00] vs 1·29 [IQR 0·51 – 2·78] ug/mL; *P*< 0·0001), FDP (66·50 [IQR 17·50–150·00]vs 4·50 [IQR 4·00–14·90] g/L; *P*< 0·0001), activated partial thromboplastin time (APTT, 38·40 [IQR 35·25–44·55] vs 37·60 [IQR 34·60 – 41·18] s; *P*= 0·033), prothrombin time (PT, 16·20 [IQR 13.80–18.20] vs 13·90 [IQR 13.30–14.70] s; *P*< 0·0001), and thrombin time (TT, 18·80 [IQR 16·68 – 21·83] vs 16·65 [IQR 15·80 – 17·60] s; *P*< 0·0001) were elevated in patients with DIC. Notably, the level of platelet (138·00 [IQR 84·00-170·00] vs 215·00 [IQR 163·00-282·00] × 10^9/L; *P*< 0·0001) and fibrinogen (2·82 [IQR 1·58 – 4·90] vs 5·06 [IQR 3·74 – 6·00] g/L; *P*< 0·0001) were significantly decreased in patients with DIC.

Table 2
laboratory findings and clinical outcomes of COVID-19 patients with DIC and without DIC

Indicators	Total	DIC	Non-DIC	p value
	N = 329	N = 59	N = 270	
Coagulation function				
Platelet, × 10^9/L (*N* = 329)	202·00(147·00-260·00)	138·00(84·00-170·00)	215·00(163·00-282·00)	**< 0·0001***
D-Dimer, ug/mL (*N*= 324)	1·49(0·59 – 4·55)	11·52(1·96 – 21·00)	1·29(0·51 – 2·78)	**< 0·0001***
APTT, s (*N*= 321)	37·70(34·70 – 42·10)	38·40(35·25– 44·55)	37·60(34·60 – 41·18)	**0·033***
FDP, g/L (*N*= 261)	6·40(4·00– 30·20)	66·50(17·50– 150·00)	4·50(4·00– 14·90)	**< 0·0001***
PT, s (*N*= 327)	14·00(13·40 – 15·10)	16.20(13.80– 18.20)	13.90(13.30– 14.70)	**< 0·0001***
TT, s (*N*= 184)	16.90(15·90 – 18·33)	18·80(16·68 – 21·83)	16·65(15·80 – 17·60)	**< 0·0001***
Fibrinogen, g/L (*N*= 321)	4·77(3·34 – 5·82)	2·82(1·58 – 4·90)	5·06(3·74 – 6·00)	**< 0·0001***
Blood routine				
Leukocyte count, $\times 10^9$/L (*N*= 329)	6·75(5·06–9·47)	9·27(5·60 – 15·45)	6·45(5·00–8·45)	**< 0·0001***
Lymphocytes, % (*N*= 329)	15·00(8·10– 23·30)	7·00(3·30 – 13·65)	17·15(9·15– 24·15)	**< 0·0001***
Neutrophils, % (*N*= 329)	75·30(65·50– 86·10)	87·90(75·40– 92·70)	74·10(64·80– 83·88)	**< 0·0001***
Eosinophils, % (*N*= 329)	0·20(0·00–1·10)	0·00(0·00–0·10)	0·35(0·00–1·30)	**< 0·0001***
Immune cell subsets				
T cells + B cells + NK cell count per μL (*N*= 96)	1101·00(610·50-1531·50)	384·50(302·50– 678·75)	1229·00(767·50-1599·25)	**< 0·0001***
CD3-CD19 + B cell count per μL (*N*= 96)	156·00(100·25– 205·75)	113·50(60·50– 156·00)	158·50(115·00-213·50)	**0·048***
CD3 + CD19- T cell count per μL (*N*= 96)	734·00(357·25-1037·25)	267·50(141·75– 396·50)	802·50(422·00-1075·25)	**< 0·0001***

Indicators	Total	DIC	Non-DIC	p value
	N = 329	N = 59	N = 270	
CD3 + CD8 + T cell count per μL (*N* = 96)	212·00(89·75–341·75)	59·50(29·75–95·00)	238·50(140·50–359·00)	**< 0·0001***
CD3-CD16 + CD56 + NK count per μL (*N* = 96)	177·50(68·00-309·50)	52·50(39·50–66·50)	203·50(108·75–316·25)	**< 0·0001***
Inflammatory cytokines and biomarkers				
IL-6, pg/mL (*N* = 271)	15·80(3·96 – 49·79)	46·33(26·56–133·50)	11·11(3·23–35·24)	**< 0·0001***
IL-10, pg/mL (*N* = 268)	5·00(5·00–9·80)	9·95(5·63 – 17·93)	5·00(5·00–7·85)	**< 0·0001***
IL-8, pg/mL (*N* = 270)	15·75(8·33 – 30·55)	32·55(16·45–61·00)	12·65(7·58 – 25·65)	**< 0·0001***
TNF-α, pg/mL (*N* = 280)	8·65(6·68 – 12·00)	11·05(8·13–15·20)	8·40(6·40 – 11·58)	**0·0010***
IL-1β, pg/mL (*N* = 269)	5·00(5·00–6·10)	5·00(5·00–7·60)	5·00(5·00–5·50)	0·29
IL-2R, U/mL (*N* = 269)	738·00(493·00-1170·00)	1200·50(825·50-1571·75)	661·00(461·50-1024·00)	**< 0·0001***
PCT, ng/mL (*N* = 304)	0·09(0·06 – 0·24)	0·21(0·11 – 0·87)	0·07(0·05 – 0·18)	**< 0·0001***
hs-CRP, mg/L (*N* = 326)	41·95(8·05-106·33)	78·70(55·90–120·90)	32·00(5·10–93·90)	**< 0·0001***
Blood gas characteristics				
PaO2, mmHg (*N* = 243)	83·00(70·45–89·70)	70·50(58·38–79·90)	84·00(74·10–90·95)	**0·00069***
SaO2, % (*N* = 243)	96·40(90·00–98·70)	86·00(77·25–91·00)	97·00(93·00–98·80)	**< 0·0001***
Organ damage indexes				
ALT, U/L (*N* = 328)	22·00(16·00–39·25)	29·00(19·50–54·00)	21·00(15·00–38·00)	**0·0021***
AST, U/L (*N* = 328)	31·00(22·00–46·00)	42·00(34·00–73·50)	28·00(20·00–42·00)	**< 0·0001***

Indicators	Total	DIC	Non-DIC	p value
	N = 329	N = 59	N = 270	
GGT, U/L (*N* = 327)	32·00(20·00–63·50)	37·00(25·00–76·50)	31·00(20·00–57·00)	**0·019***
TBIL, umol/L (*N* = 329)	10·40(7·60 – 15·20)	13·80(10·30 – 20·95)	9·80(7·30 – 13·88)	**< 0·0001***
ALB, g/L (*N* = 327)	33·67 ± 5·01	31·69 ± 4·51	34·11 ± 5·02	**0·00075***
LDH, U/L (*N* = 309)	335·00(238·00-493·00)	591·00(391·00-788·00)	301·50(219·50–458·25)	**< 0·0001***
ALP, U/L (*N* = 310)	71·00(57·00–89·00)	85·00(57·00-118·00)	69·00(56·50–84·00)	**0·014***
CK, U/L (*N* = 238)	73·50(44·25–137·50)	216·00(109·50–421·00)	64·00(40·50–105·00)	**< 0·0001***
CK-MB, U/L (*N* = 249)	1·00(0·60 – 2·30)	2·60(1·30 – 6·60)	0·95(0·60 – 1·80)	**< 0·0001***
ICU admission				
ICU	65/314 (20·70%)	38/58 (65·52%)	27/256 (10·55%)	**< 0·0001***
Non-ICU	249/314 (79·30%)	20/58 (34·48%)	229/256 (89·45%)	··
Outcomes	N = 329	N = 59	N = 270	
Survivor	217(65·96%)	5(8·47%)	212(78·52%)	**< 0·0001***
Non-survivor	112(34·04%)	54(91·53%)	58(21·48%)	··

Abbreviation:COVID-19, Coronavirus disease 2019; DIC, Disseminated intravascular coagulation; APTT, Activated partial thromboplastin time; FDP, Fibrin degradation products; PT, Prothrombin time; TT, Thrombin time; CD, Cluster of differentiation; NK cells, Natural killer cells; IL-6, Interleukin 6; IL-10, Interleukin 10; IL-8, Interleukin 8; TNF-α, Tumor necrosis factor α; IL-1β, Interleukin 1β; IL-2R, Interleukin 2 receptor; PCT, Procalcitonin; hs-CRP, Hypersensitive C-reactive protein; PaO2, Oxygen partial pressure; SaO2, Oxygen saturation; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; GGT, Gamma-glutamyl transpeptidase; TBIL, Total bilirubin; ALB, Albumin; LDH, Lactate dehydrogenase; ALP, Alkaline phosphatase; CK, Creatine kinase; CK-MB, Creatine kinase isoenzyme, ICU, Intensive care unit.

Continuous variables were described as median and interquartile range (IQR) or mean and standard deviation (SD). *P* values were calculated by Analysis of Student's t test for normal distribution data or Mann-Whitney U test for skewed distributed data. * *P* < 0·05.

Furthermore, we found that aggravated inflammatory responses and dysregulated immune cells presented in patients with DIC (Table 2). The inflammatory biomarkers including interleukin-6 (IL-6, 46·33

[IQR 26·56–133·50] vs 11·11 [IQR 3·23–35·24] pg/mL; *P* < 0·0001), tumor necrosis factor-α (TNF-α, 11·05 [IQR 8·13–15·20] vs 8·40 [IQR 6·40 – 11·58] pg/mL; *P* = 0·0010), IL-10 (9·95 [IQR 5·63 – 17·93] vs 5·00 [IQR 5·00–7·85] pg/mL; *P* < 0·0001), IL-8 (32·55 [IQR 16·45–61·00] vs 12·65 [IQR 7·58 – 25·65] pg/mL; *P* < 0·0001), interleukin 2 receptor (IL-2R, 1200·50 [IQR 825·50-1571·75] vs 661·00 [IQR 461·50-1024·00] U/mL; *P* < 0·0001), procalcitonin (PCT, 0·21 [IQR 0·11 – 0·87] vs 0·07 [IQR 0·05 – 0·18] ng/mL; *P* < 0·0001), and hypersensitive C-reactive protein (hs-CRP, 78·70 [IQR 55·90–120·90] vs 32·00 [IQR 5·10–93·90] mg/L; *P* < 0·0001) were significantly increased in patients with DIC. In contrast, in terms of immune cells, patients with DIC had decreased lymphocytes (7·00 [IQR 3·30 – 13·65] vs 17·15 [IQR 9·15–24·15] %; *P* < 0·0001), the total number of T cells, B cells and NK cells (384·50 [IQR 302·50–678·75] vs 1229·00 [IQR 767·50-1599·25] /uL; *P* < 0·0001), CD8 + T cells (59·50 [IQR 29·75–95·00] vs 238·50 [IQR 140·50–359·00] /uL; *P* < 0·0001), CD3 + CD19- T cell (267·50 [IQR 141·75–396·50] vs 802·50 [IQR 422·00-1075·25] /uL; *P* < 0·0001), CD3-CD19 + B cells (113·50 [IQR 60·50–156·00] vs 158·50 [IQR 115·00-213·50] /uL; *P* = 0·048), and CD3-CD16 + CD56 + NK cells (52·50 [IQR 39·50–66·50] vs 203·50 [IQR 108·75–316·25] /uL; *P* < 0·0001).

We also observed substantial differences in organ damage indexes between these two groups, especially in liver and heart impairment-related indicators (Table 2). The level of alanine aminotransferase (ALT, 29·00 [IQR 19·50–54·00] vs 21·00 [IQR 15·00–38·00] U/L; *P* = 0·0021), aspartate aminotransferase (AST, 42·00 [IQR 34·00–73·50] vs 28·00 [IQR 20·00–42·00] U/L; *P* < 0·0001), total bilirubin (TBIL, 13·80 [IQR 10·30 – 20·95] vs 9·80 [IQR 7·30 – 13·88] umol/L; *P* < 0·0001), alkaline phosphatase (ALP, 85·00 [IQR 57·00-118·00] vs 69·00 [IQR 56·50–84·00] U/L; *P* = 0·014), lactate dehydrogenase (LDH, 591·00 [IQR 391·00-788·00] vs 301·50 [IQR 219·50–458·25] U/L; *P* < 0·0001), creatine kinase (CK, 216·00 [IQR 109·50–421·00] vs 64·00 [IQR 40·50–105·00] U/L; *P* < 0·0001) and creatine kinase isoenzyme (CK-MB, 2·60 [IQR 1·30 – 6·60] vs 0·95 [IQR 0·60 – 1·80] U/L; *P* < 0·0001) were higher in patients with DIC. Notably, albumin (ALB, 31·69 ± 4·51 vs 34·11 ± 5·02 g/L; *P* < 0·00075) was markedly reduced in patients with DIC. For blood routine results, patients with DIC had elevated leukocyte count (9·27 [IQR 5·60 – 15·45] vs 6·45 [IQR 5·00–8·45] × 10^9; *P* < 0·0001), elevated neutrophils (87·90 [IQR 75·40–92·70] vs 74·10 [IQR 64·80–83·88] %; *P* < 0·0001) and reduced eosinophils (0 [IQR 0·00–0·10] vs 0·35 [IQR 0·00–1·30] %; *P* < 0·0001). Additionally, we found that patients with DIC had aggravated hypoxia. The partial pressure of oxygen level (PaO2, 70·50 [IQR 58·38–79·90] vs 84·00 [IQR 74·10–90·95] mmHg; *P* = 0·00069) and oxyhemoglobin saturation (SaO2, 86·00 [IQR 77·25–91·00] vs 97·00 [IQR 93·00–98·80] %; *P* < 0·0001) were decreased in patients with DIC. The results are shown in Table 2.

Besides, 38 (65·52%) of the 58 patients with DIC were admitted to ICU, comparing to 27 (10·55%) of the 256 patients without DIC (*P* < 0·0001). It was noted that patients with DIC had a higher proportion of death (54 of 59 [91·53%] vs 58 of 270 [21·48%]; *P* < 0·0001, Table 2). These findings suggest that patients with DIC had aggravated coagulation dysfunction, inflammatory responses, dysregulated immune cells, and liver damage, which were related to poor clinical outcomes.

Complications and clinical treatments of COVID-19 patients with DIC and without DIC

As summarized in Table 3, the infection of SARS-CoV-2 could cause pulmonary and multi-system inflammation, and finally lead to serious complications. ARDS (57 [96·61%] vs 171 [63·33%]; *P*< 0·0001), acute liver injury (26 [44·07%] vs 16 [5·93%]; *P*< 0·0001), heart failure (48 [81·36%] vs 63 [23·33%]; *P*< 0·0001) and cardiac injury (53 [89·83%] vs 81 [30·00%]; *P*< 0·0001) were more common in patients with DIC.

Table 3
Clinical treatments and complications of COVID-19 patients with DIC and without DIC

Indicators	Total	Patients with DIC	Patients without DIC	p value
	N = 329	N = 59	N = 270	
Complications				
Acute liver injury	42(12·77%)	26(44·07%)	16(5·93%)	**< 0·0001***
Heart failure	111(33·74%)	48(81·36%)	63(23·33%)	**< 0·0001***
Cardiac injury	134(40·73%)	53(89·83%)	81(30·00%)	**< 0·0001***
ARDS	228(69·30%)	57(96·61%)	171(63·33%)	**< 0·0001***
Treatment[λ]				
Antiviral therapy	156(47·42%)	30(50·85%)	126(46·67%)	0·56
Antibiotics	283(86·02%)	57(96·61%)	226(83·70%)	**0·010***
Intravenous immunoglobulin therapy	145(44·07%)	42(71·19%)	103(38·15%)	**< 0·0001***
Glucocorticoid therapy	201(61·09%)	56(94·92%)	145(53·70%)	**< 0·0001***
High-flow oxygen therapy	165(50·15%)	13(22·03%)	152(56·30%)	**< 0·0001***
Mechanical ventilation	86(26·14%)	45(76·27%)	41(15·19%)	**< 0·0001***
Non-invasive	37(11·25%)	18(30·15%)	19(7·04%)	**< 0·0001***
Invasive	49(14·89%)	27(45·76%)	22(8·15%)	**< 0·0001***
ECOM	4(1·22%)	4(6·78%)	0	**0·00095***[a]
Transfusion	88(26·75%)	42(71·19%)	46(17·04%)	**< 0·0001***

Abbreviation: COVID-19, Coronavirus disease 2019; ARDS, Acute respiratory distress syndrome; DIC, Disseminated intravascular coagulation; ECOM, Extracorporeal membrane oxygenation.

[λ] Treatments include antibiotics (cephalosporin, fluoroquinolones or macrolides), antiviral therapy (lopinavir/ritonavir, ganciclovir, riboviron or oseltamivir) or transfusion (suspended red blood cells, platelets or plasma).

Categorical variables were expressed as number (%). *P* values were calculated by Fisher's exact test (a) or Pearson $\chi 2$ test. *$P < 0.05$.

In terms of clinical treatments (Table 3), antibiotics (57 [96·61%] vs 226 [83·70%]; $P = 0·010$), intravenous immunoglobulin therapy (42 [71·19%] vs 103 [38·15%]; $P < 0·0001$) and glucocorticoid therapy (56 [94·92%] vs 145 [53·70%]; $P < 0·0001$) were more frequently used in patients with DIC. Besides, the ventilation treatment was the conventional non-drug therapy and patients with DIC received more non-

invasive mechanical ventilation (18 [30·15%] vs 19 [7·04%]; *P* < 0·0001) and invasive mechanical ventilation (27 [45·76%] vs 22 [8·15%]; *P* < 0·0001). Of note, transfusion (42 [71·19%] vs 46 [17·04%]; *P* < 0·0001) and extracorporeal membrane oxygenation (ECMO, 4 [6·78%] vs 0 [0·00%]; *P* = 0·00095) were significantly more prevalent in patients with DIC.

Risk factors associated with the development of DIC in COVID-19 patients

Furthermore, multivariate logistic models were applied to explore risk factors associated with the development of DIC in COVID-19 patients with adjustment of age, gender, and comorbidities. As shown in Table 4, we found that the elevated level of D-Dimer (OR = 1·146, 95%CI = 1·100-1·194; *P* < 0·0001), FDP (OR = 1·027, 95%CI = 1·019 − 1·036; *P* < 0·0001), APTT (OR = 1·097, 95%CI = 1·041 − 1·155; *P* = 0·00051), PT (OR = 1·851, 95%CI = 1·516-2·258; *P* < 0·0001) and TT (OR = 1·214, 95%CI = 1·088 − 1·356; *P* = 0·00055) presented higher risks for the development of DIC in COVID-19 patients. Conversely, decreased platelet (OR = 0·986, 95%CI = 0·982-0·991; *P* < 0·0001) and fibrinogen (OR = 0·476, 95%CI = 0·380-0·596; *P* < 0·0001) were significantly associated with the development of DIC in COVID-19 patients.

Table 4
Factors associated with the development of DIC in COVID-19 patients

Indicators	Univariable logistic regression		Multivariable logistic regression	
	OR (95% CI)	p value	OR (95% CI)	p value
Coagulation function				
Platelet, × 10^9/L (*N* = 329)	0·986(0·981-0·990)	**< 0·0001***	0·986(0·982-0·991)	**< 0·0001***
D-Dimer, ug/mL (*N* = 324)	1·149(1·104-1·196)	**< 0·0001***	1·146(1·100-1·194)	**< 0·0001***
APTT, s (*N* = 321)	1·096(1·044 – 1·151)	**0·00025***	1·097(1·041 – 1·155)	**0·00051***
FDP, g/L (*N* = 261)	1·025(1·017 – 1·032)	**< 0·0001***	1·027(1·019 – 1·036)	**< 0·0001***
PT, s (*N* = 327)	1·772(1·483-2·118)	**< 0·0001***	1·851(1·516-2·258)	**< 0·0001***
TT, s (*N* = 184)	1·192(1·070 – 1·329)	**0·0015***	1·214(1·088 – 1·356)	**0·00055***
Fibrinogen, g/L (*N* = 321)	0·492(0·398-0·609)	**< 0·0001***	0·476(0·380-0·596)	**< 0·0001***
Blood routine				
Leukocyte count, $\times 10^9$/L (*N* = 329)	1·181(1·106-1·261)	**< 0·0001***	1·196(1·113-1·284)	**< 0·0001***
Lymphocytes, % (*N* = 329)	0·906(0·871-0·943)	**< 0·0001***	0·906(0·870-0·944)	**< 0·0001***
Neutrophils, % (*N* = 329)	1·060(1·033 – 1·088)	**< 0·0001***	1·058(1·030 – 1·087)	**< 0·0001***
Eosinophils, % (*N* = 329)	0·159(0·063 – 0·402)	**0·00010***	0·177(0·072 – 0·435)	**0·00016***
Immune cell subsets				
T cells + B cells + NK cell count per μL (*N* = 96)	0·997(0·995-0·999)	**0·0012***	0·996(0·993-0·998)	**0·0015***
CD3-CD19 + B cell count per μL (*N* = 96)	0·992(0·984-1·001)	0·068	0·983(0·968-0·997)	**0·017***
CD3 + CD19- T cell count per μL (*N* = 96)	0·996(0·994-0·999)	**0·0025***	0·995(0·992-0·998)	**0·0029***

Indicators	Univariable logistic regression		Multivariable logistic regression	
	OR (95% CI)	p value	OR (95% CI)	p value
CD3 + CD8 + T cell count per μL (*N* = 96)	0·984(0·974-0·994)	**0·0018***	0·979(0·966-0·992)	**0·0022***
CD3-CD16 + CD56 + NK count per μL (*N* = 96)	0·984(0·974-0·995)	**0·0035***	0·982(0·969-0·995)	**0·0080***
Inflammatory cytokines and biomarkers				
IL-6, pg/mL (*N* = 271)	1·010(1·005 − 1·014)	**< 0·0001***	1·010(1·005 − 1·015)	**0·00017***
IL-10, pg/mL (*N* = 268)	1·010(0·996-1·023)	0·16	1·012(0·997-1·028)	0·12
IL-8, pg/mL (*N* = 270)	1·008(1·003 − 1·013)	**0·0027***	1·008(1·002 − 1·014)	**0·0052***
TNF-α, pg/mL (*N* = 280)	1·048(1·015 − 1·082)	**0·0040***	1·053(1·016 − 1·091)	**0·0045***
IL-1β, pg/mL (*N* = 269)	1·005(0·961-1·050)	0·84	1·014(0·961-1·070)	0·61
IL-2R, U/mL (*N* = 269)	1·001(1·001–1·002)	**< 0·0001***	1·001(1·001–1·002)	**< 0·0001***
PCT, ng/mL (*N* = 304)	1·088(0·927-1·277)	0·30	1·034(0·868-1·231)	0·71
hs-CRP, mg/L (*N* = 326)	1·008(1·004 − 1·012)	**< 0·0001***	1·008(1·004 − 1·012)	**< 0·0001***
Blood gas characteristics				
PaO2, mmHg (*N* = 243)	0·971(0·950-0·992)	**0·0069***	0·969(0·948-0·990)	**0·0047***
SaO2, % (*N* = 243)	0·966(0·946-0·987)	**0·0014***	0·965(0·943-0·987)	**0·0017***
Organ damage indexes				
ALT, U/L (*N* = 328)	1·012(1·003 − 1·021)	**0·0087***	1·011(1·002 − 1·020)	**0·020***
AST, U/L (*N* = 328)	1·023(1·013 − 1·033)	**< 0·0001***	1·023(1·013 − 1·034)	**< 0·0001***
GGT, U/L (*N* = 327)	1·003(0·999-1·006)	0·10	1·003(0·999-1·006)	0·12

Indicators	Univariable logistic regression		Multivariable logistic regression	
	OR (95% CI)	p value	OR (95% CI)	p value
TBIL, umol/L (*N* = 329)	1·069(1·035 − 1·104)	< 0·0001*	1·070(1·034 − 1·107)	0·00012*
ALB, g/L (*N* = 327)	0·902(0·848-0·959)	0·0010*	0·901(0·845-0·961)	0·0015*
LDH, U/L (*N* = 309)	1·005(1·004 − 1·007)	< 0·0001*	1·005(1·004 − 1·007)	< 0·0001*
ALP, U/L (*N* = 310)	1·010(1·004 − 1·017)	0·0024*	1·011(1·004 − 1·018)	0·0017*
CK, U/L (*N* = 238)	1·001(1·000–1·002)	0·0053*	1·001(1·000–1·002)	0·014*
CK-MB, U/L (*N* = 249)	1·093(1·040 − 1·148)	0·00044*	1·089(1·035 − 1·145)	0·00098*
Abbreviation: COVID-19, Coronavirus disease 2019; DIC, Disseminated intravascular coagulation; OR, Odds ratio; CI, Confidential interval; APTT, Activated partial thromboplastin time; FDP, Fibrin degradation products; PT, Prothrombin time; TT, Thrombin time; CD, Cluster of differentiation; NK cells, Natural killer cells; IL-6, Interleukin 6; IL-10, Interleukin 10; IL-8, Interleukin 8; TNF-α, Tumor necrosis factor-α; IL-1β, Interleukin 1β; IL-2R, Interleukin 2 receptor; PCT, Procalcitonin; hs-CRP, Hypersensitive C-reactive protein; PaO2, Oxygen partial pressure; SaO2, Oxygen saturation; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; GGT, Gamma-glutamyl transpeptidase; TBIL, Total bilirubin; ALB, Albumin; LDH, Lactate dehydrogenase; ALP, Alkaline phosphatase; CK, Creatine kinase; CK-MB, Creatine kinase isoenzyme.				
ORs and 95% CIs were calculated by univariable logistic regression models. *P < 0·05.				

Additionally, inflammatory cytokines such as IL-6 (OR = 1·010, 95%CI = 1·005 − 1·015; P = 0·00017), TNF-α (OR = 1·053, 95%CI = 1·016 − 1·091; P = 0·0045), IL-8 (OR = 1·008, 95%CI = 1·002 − 1·014; P = 0·0052), IL-2R (OR = 1·001, 95%CI = 1·001–1·002; P < 0·0001), and hs-CRP (OR = 1·008, 95%CI = 1·004 − 1·012; P < 0·0001) were remarkably associated with the increased risk of the development of DIC. Inversely, declined immunes cell subsets such as lymphocytes (OR = 0·906, 95%CI = 0·870-0·944; P < 0·0001), the total number of T cells, B cells and NK cells (OR = 0·996, 95%CI = 0·993-0·998; P = 0·0015), CD3-CD19 + B cells (OR = 0·983, 95%CI = 0·968-0·997; P = 0·017), CD3 + CD19- T cell (OR = 0·995, 95%CI = 0·992-0·998; P = 0·0029), $CD8^+$ T cells (OR = 0·979, 95%CI = 0·966-0·992; P = 0·0022), and CD3-CD16 + CD56 + NK cells (OR = 0·982, 95%CI = 0·969-0·995; P = 0·0080), were associated with the development of DIC.

Moreover, the elevated level of organ damage indexes, such as ALT (OR = 1·011, 95%CI = 1·002 − 1·020; P = 0·020), AST (OR = 1·023, 95%CI = 1·013 − 1·034; P < 0·0001), TBIL (OR = 1·070, 95%CI = 1·034 − 1·107; P = 0·00012), ALP (OR = 1·011, 95%CI = 1·004 − 1·018; P = 0·0017), LDH (OR = 1.005, 95%CI = 1·004 − 1·007; P < 0·0001), CK(OR = 1·001, 95%CI = 1·000–1·002; P = 0·014) and CK-MB (OR = 1·089, 95%CI = 1·035 − 1·145; P < 0·00098), were related to increased risk of the development of DIC, whereas the level of ALB

(OR = 0·901, 95%CI = 0·845-0·961; *P* = 0·0015) was inversely associated with the risk of the development of DIC. For blood gas characteristics, decreased PaO2 (OR = 0·969, 95%CI = 0·948-0·990; *P* = 0·0047) and SaO2 (OR = 0·965, 95%CI = 0·943-0·987; *P* = 0·0017) were significantly correlated with the higher risk of the development of DIC.

Discussion

In the single-centered, retrospective, and observational study from Tongji Hospital, we found that patients with DIC had a higher risk of death compared to patients without DIC. Moreover, in addition to previously reported coagulation-related markers, such as FDP, D-dimer, and platelet, we identified several risk factors associated with DIC development including elevated IL-6 and TNF-α as well as decreased fibrinogen and ALB. The risk factors related to DIC development would be of great value in the early identification of severe cases.

59 enrolled COVID-19 patients with DIC and 270 enrolled COVID-19 patients without DIC were statistically matched based on age, gender, and comorbidities. We observed that patients with DIC presented aggravated coagulation dysfunction, inflammation response, dysregulated immune cells, and liver damage. These findings provided supporting evidence that COVID-19 patients combined DIC were likely to have a higher proportion of death.

Furthermore, we used multivariable logistic regression models to explore the risk factors related to DIC development in COVID-19 patients. Consistent with the previous study, we found that the coagulation-related markers such as FDP, D-dimer, and platelet were associated with the development of DIC in COVID-19 patients. D-dimer originates from the formation and lysis of cross-linked fibrin,[8] and FDP is the degradation product of fibrinogen and fibrin.[9] The levels of fibrin-related markers such as D-dimer and FDP moderately or markedly elevated after the coagulation activation and fibrinolysis stimulation.[5] Therefore, an overproduction of D-dimer and FDP indicated the hypercoagulable and hyperfibrinolysis state in COVID-19 patients.[10] Additionally, abnormalities in PT, APTT, TT, and platelet are relatively common in presentations of patients with DIC. The decreased platelet and elevated PT, APTT, and TT were the indicators of the increased secretion of anticoagulants and dysfunction of bleeding, which reflected the physiologic decompensation, organ malfunction, and the development of intravascular coagulopathy evolving towards DIC.[11,12] Of note, fibrinogen, a novel risk factor identified in this study, was a glycoprotein synthesized in the liver.[13] Fibrinogen is important for hemostasis because of its critical role in platelet aggregation and fibrin clot formation, besides fibrinogen protect thrombin from decay in the process of thrombosis.[9,14] In addition, the decreased level of fibrinogen could be the biomarker of hyperfibrinolysis and hemorrhagic conditions.[15] These abnormal coagulation parameters were more severe in COVID19 patients with DIC, which might partly attribute to high mortality in the particular population.[5,10,15]

We also found that dysregulated immune cells and aggravated inflammatory responses such as IL-6, IL-8, TNF-α, IL-2R, hs-CRP, neutrophil, and leukocyte, were more pronounced in COVID-19 patients with DIC than

those without DIC. The constant stimulation of the virus infection can induce T cell exhaustion and facilitate a dysregulated immune response, ultimately triggering the pro-inflammatory cytokine responses.[16] In addition, this hyperinflammatory state could activate platelets, stimulate fibrinolysis, and predispose to ischemia and thrombosis by limiting endothelial cells' function and excessively generation of thrombin.[17] Among the measured cytokines, IL-6 participated in the regulation of complement activation and vascular leakage.[18] TNF-α acted as an essential part in airway hyper-responsiveness and mediated the pathogenesis of influenza and SRAS-CoV infection.[19] Moreover, TNF-α and IL6 activate vascular endothelial cells and the coagulation pathway through inducing the expression of tissue factor and downregulating thrombomodulin on endothelial surfaces.[20,21] Furthermore, in line with the previous studies, IL-6 and TNF-α were both related to poor outcomes for COVID-19 patients.[22] However, it remains insufficient to explore the association between the pro-inflammatory responses and coagulation function.

Expect for typical coagulation dysfunction and aggravated inflammatory storm, liver damage appeared to be another feature in COVID-19 patients with DIC. We found that liver injury-related factors such as ALT, AST, ALP, TBIL, LDH, and ALB were abnormally dysregulated in patients with DIC. It is known that the liver plays a significant part in the coagulation system and synthesizes various coagulation factors such as fibrinogen and prothrombin.[23] Recent research had reported that acute liver injury and chronic liver disease were correlated with coagulation dysfunction.[24] The declined ALB was pronounced among the liver injury-related factors and identified as a significant independent predictor factor of thrombotic risk. Remarkably, ALB not only maintains the colloid osmotic pressure and blood concentration but also binds with anticoagulation factors.[25] Furthermore, the decreased level of ALB suggests the hypercoagulable state and blood clots condition, which increases the risk of adverse clinical outcomes in COVID-19 patients.[26] In addition, we found that some patients with DIC had hypoxia on admission. Hypoxia deregulates platelet function through enhancement of platelet adhesion, aggregation, and release, which ultimately activates intravascular coagulation and causes the formation of thrombus.[27] Collectively, these findings indicated that the combination of coagulation dysfunction, aggravated inflammatory responses and liver damage in patients with DIC might be explicable mechanisms of worse prognosis, which caused complications such as ARDS and acute liver injury.[28,29]

Standardized treatment protocols are essential for COVID-19 patients, especially in severe cases. Consistent with other studies, antibiotics and antivirals were widely used in COVID-19 treatment. Moreover, we found that patients with DIC had more glucocorticoid therapy, immunoglobulin therapy, mechanical ventilation, transfusion, and ECOM, in line with recent studies that severe COVID-19 patients tended to have more clinical interventions.[2,28] Preliminary evidence suggests that the treatment of anticoagulant and anti-inflammatory such as low molecular weight heparin is effective treatments for severe COVID-19 patients with coagulation dysfunction at present.[17] In addition, considering impaired adaptive immune responses, liver damage, and deleterious complications in patients with DIC, protection treatment for liver function and complications as well as supportive care should be focused on the current management of COVID-19.

In our study, three major strategies are warranted for patients with DIC during this COVID-19 crisis. First, coagulation parameters should be dynamically monitored for early detection and prevention of the development of DIC in COVID-19 patients. Second, treatments for inflammation and coagulation should be considered in COVID-19 patients with coagulation dysfunction. Supporting therapy such as ventilation treatment is also of vital importance for COVID-19 patients with DIC, especially for severe cases. Finally, different anticoagulant treatments should be given according to the clinical stages of DIC.

There are several limitations in our study. First, it was a single-center observational study and limited the generalization of our findings. The results need to be further confirmed in additional validation sets. Second, this was a retrospective study, and not all laboratory tests were done in all patients. The interpretation of the results might be affected by the missing data. Finally, further investigation should be performed to study the link between dysregulated inflammatory cytokines and coagulation dysfunction and the potential mechanisms of liver damage for coagulation dysfunction.

In summary, through the single-centered, retrospective, and observational study, we demonstrated the clinical characteristics of the patients with DIC. In addition to previously reported markers D-Dimer, FDP, and platelet, our study identified several novel risk factors including decreased fibrinogen, elevated IL-6, elevated TNF-α, and decreased ALB, which were associated with the development of DIC in COVID-19 patients.

Abbreviations

COVID-19, Coronavirus disease 2019; DIC, Disseminated intravascular coagulation; SARS-CoV-2, syndrome coronavirus 2; ICU, Intensive care unit; RT-PCR, Reverse transcription polymerase chain reaction; ISTH, International society on thrombosis and hemostasis; SSC, Subcommittee of the scientific and Standardization Committee; FDP, Fibrin degradation products; APTT, Activated partial thromboplastin time; CT, Chest computed tomographic; PT, Prothrombin time; TT, Thrombin time; IL-6, Interleukin 6; IL-10, Interleukin 10; IL-8, Interleukin 8; TNF-α, Tumor necrosis factor α; IL-2R, Interleukin 2 receptor; PCT, Procalcitonin; hs-CRP, Hypersensitive C-reactive protein; NK cells, Natural killer cells; CD, Cluster of differentiation; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; TBIL, Total bilirubin; LDH, Lactate dehydrogenase; ALP, Alkaline phosphatase; ALB, Albumin; CK, Creatine kinase; CK-MB, Creatine kinase isoenzyme; PaO2, Oxygen partial pressure; SaO2, Oxygen saturation; ARDS, Acute respiratory distress syndrome; ECOM, Extracorporeal membrane oxygenation; IQR, Interquartile range; SD, Standard deviation; OR, Odds ratio; CI, Confidence interval.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Tongji Hospital, Tongji Medical College, HUST, and granted a waiver of informed consent from study participants.

Consent for publication

Not applicable.

Availability of data and materials

The datasets obtained and analyzed in the current study are available from the corresponding author on reasonable request.

Competing interests

The authors report no conflicts of interest.

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Authors' contributions

HC, KH, XW, JT, and YX were the overall principal investigators in this study who conceived the study and obtained financial support, were responsible for the study design, and supervised the entire study. ZY, JW, JX, QL, and CL recruited participants. MJ, XY, SZ, YW, ZL, ZY, and JW drafted the paper. JT, XY, and MJ completed the statistical analyses. SZ, YW, ZL, ZY, and JW completed data analysis, interpreted the results. JX, QL, CL, HC, KH, XW, and YX reviewed the manuscript. All authors participated in interpretation data, manuscript writing, and review of the manuscript. Besides, All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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