Since December 2019, the severity of the coronavirus disease 2019 (COVID-19) pandemic has been escalating.\(^1\) Coagulopathy is common in critically ill patients with COVID-19.\(^2\) Systemic microvascular thrombosis may occur in most deaths, and was corroborated by a recent autopsy.\(^3\) However, less is known about the coagulation parameter D-dimer in the progression of COVID-19. In this study, we describe 279 COVID-19 patients recruited from three hospitals in Hubei Province, China and investigate the dynamic relationship between D-dimer level and the progression of COVID-19.

According to COVID-19 Diagnosis and Treatment Scheme (Trial Version 7),\(^4\) all laboratory-confirmed COVID-19 patients were mild and moderate cases on admission in our study. We further divided them into three groups according to their clinical courses: an ordinary group (disease was mild or subsided, \(n = 136\)), an improved group (disease

**Table I.** Baseline characteristics and laboratory findings of patients infected with COVID-19 on admission.

| Characteristics               | Total (\(n = 279\)) | Ordinary (\(n = 136\)) | Improved (\(n = 23\)) | Poor (\(n = 120\)) | \(P\)   |
|------------------------------|---------------------|-------------------------|-----------------------|---------------------|--------|
| Age, median (IQR), years     | 55 (39–68)          | 49 (36–56)              | 58 (41.5–67.5)        | 65 (51–72)          | <0.001 |
| Sex                          |                     |                         |                       |                     |        |
| Male                         | 149 (53–4)          | 66 (48–5)               | 12 (52–2)             | 71 (59–2)           | 0.31   |
| Female                       | 126 (45–2)          | 67 (50–3)               | 10 (45–3)             | 49 (40–8)           |        |
| Cardiovascular disease       | 77 (27–6)           | 25 (18–4)               | 1 (4–3)               | 51 (42–5)           | <0.001 |
| Respiratory disease          | 29 (10–4)           | 10 (7–4)                | 1 (4–3)               | 18 (15–0)           | 0.08   |
| Immune disease               | 7 (2–5)             | 3 (2–2)                 | 0 (0–0)               | 4 (3–3)             | 0.61   |
| Endocrine disease            | 35 (12–5)           | 12 (8–8)                | 1 (4–3)               | 22 (18–3)           | 0.03   |
| Tumour                       | 3 (1–1)             | 1 (0–7)                 | 0 (0–0)               | 2 (1–7)             | 0.67   |
| Infectious disease           | 9 (3–2)             | 2 (1–3)                 | 1 (4–3)               | 6 (5–0)             | 0.27   |
| Signs and symptoms           |                     |                         |                       |                     |        |
| Fever                        | 217 (77–8)          | 106 (77–9)              | 17 (73–9)             | 94 (78–3)           | 0.53   |
| Cough                        | 191 (68–5)          | 99 (72–8)               | 17 (73–9)             | 75 (62–5)           | 0.54   |
| Chest tightness              | 31 (11–1)           | 16 (11–8)               | 1 (4–3)               | 14 (11–7)           | 0.15   |
| Shortness of breath          | 24 (8–6)            | 7 (5–1)                 | 3 (13–0)              | 14 (11–7)           | 0.02   |
| Fatigue                      | 60 (21–5)           | 27 (20–9)               | 9 (39–1)              | 24 (20–0)           | 0.13   |
| Heart rate, median (IQR), bpm| 86 (80–98)          | 86 (80–98)              | 87.5 (72–95)          | 88 (80–98)          | 0.26   |
| SBP, median (IQR), mm Hg     | 125 (119–137)       | 125 (118–136–5)         | 121 (116–130)         | 126 (120–139)       | 0.73   |
| DBP, median (IQR), mm Hg     | 78 (70–86)          | 80 (76–87–5)            | 79 (70–85)            | 75 (70–80)          | <0.001 |
| Respiratory rate, median (IQR)| 20 (19–22)          | 20 (18–20)              | 20 (20–22)            | 20 (20–25)          | <0.001 |
| Laboratory indexens median (IQR) |                     |                         |                       |                     |        |
| White blood cell count, ×10^9/l | 5.0 (4.0–7.9)       | 4.2 (3.6–5.2)           | 4.8 (4.1–8.0)         | 6.6 (4.5–8.6)       | <0.001 |
| Lymphocyte count, ×10^9/l    | 9 (0.6–1.3)         | 1.2 (0.9–1.6)           | 0.7 (0.7–1.3)         | 0.8 (0.5–1.1)       | <0.001 |
| Lactate dehydrogenase, u/l   | 263.0 (179.0–360.0) | 186.0 (164.0–233.5)     | 277.0 (190.0–297.5)   | 335.0 (227.0–408.0) | <0.001 |
| Alanine transaminase, u/l    | 23.0 (16.8–36.5)    | 23.0 (17.8–30.5)        | 21.0 (19.0–72.0)      | 25.0 (16.0–50.0)    | <0.01   |
| Aspartate transaminase, u/l  | 27.0 (18.0–45.5)    | 22.0 (17.5–33.0)        | 27.0 (23.5–48.0)      | 33.0 (18.0–49.0)    | 0.14    |
| Creatinine, μmol/l           | 73.2 (60.5–92.5)    | 77.0 (64.4–94.0)        | 54.9 (48.0–68.0)      | 73.9 (63.5–95.0)    | 0.16    |
| Carbohydr, mmol/l            | 5.3 (4.1, 6.9)      | 4.8 (3.9, 6.5)          | 4.4 (3.3, 5.0)        | 5.9 (4.9, 8.2)      | 0.17    |
| D-dimer, μg/ml               | 0.3 (0.1–1.3)       | 0.2 (0.1–0.4)           | 0.8 (0.6–7.3)         | 0.6 (0.2–5.0)       | <0.01   |
worsened first and improved gradually after treatment, \( n = 23 \) m and a poor group (disease worsened and deaths, \( n = 120 \)). On admission, the epidemiological data, co-morbidities and clinical symptoms of patients were obtained (Table I). Then, we tested the coagulation profile for 10 consecutive days after admission.

As shown in Table I, median age of the 279 enrolled patients was 55.0 [interquartile range (IQR) 39.0–68.0]; it was highest in the poor group, followed by the improved group. Cardiovascular disease \([n = 77 (27.6\%)]\), respiratory disease \([n = 29 (10.4\%)]\), and endocrine disease \([n = 35 (12.5\%)]\) were the most common co-morbidities.

Infection-induced coagulopathy and secondary hyper-fibrinolysis has been identified in severe cases of COVID-19.5 In addition, a higher D-dimer level on admission was related to a worse prognosis of COVID-19.6 Thus, we tracked the variation in D-dimer levels for ten consecutive days. Based on random forests, the Gini index on Day 1 was obviously higher than that on the other days in the three groups (Fig 1A). On admission, D-dimer level was higher in the improved and poor groups than that in the ordinary group. The level decreased gradually in the improved group, but remained high in the poor group as the disease deteriorated (Fig 1B). The results were further adjusted and examined with a multinomial logistic regression model. As shown in Fig 1C, on admission, compared with the ordinary group, the improved group and the poor group demonstrated an odds ratio (OR) of 1.42 [95% consistency index (CI): 1.04, 1.96; \( P = 0.03 \)] and 1.35 (95% CI: 1.02, 1.80; \( P = 0.04 \)), respectively (Table SI).

Further, we separated the ten days into three stages: (i) Stage 1: Day 1; (ii) Stage 2: Days 2–5; (iii) Stage 3: Days 6–10. At Stage 1, the OR of the ordinary group [0.25 (95% CI: 0.16, 0.37; \( P < 0.001 \)] was obviously different from that of the poor group [0.93 (95% CI: 0.78, 1.10; \( P = 0.37 \)] (Fig 1D, E). From Stage 1 to Stage 2, D-dimer level increased with disease progression in the poor group [1.60 (95% CI: 1.28, 2.00; \( P < 0.001 \)], but not in the ordinary group [1.19 (95% CI: 0.97, 1.46; \( P = 0.09 \)] (Fig 1D, E). The same trend was also observed from Stage 2 to Stage 3, and the OR of the ordinary group and the poor group was 1.25 (95% CI: 1.07, 1.47; \( P = 0.07 \), and 1.71 (95% CI: 1.43, 2.05;
Pulmonary thrombosis is mostly responsible for the elevation of D-dimer in severe cases. Although more evidence is needed, our finding is meaningful for the establishment of early diagnosis and dynamic intervention.

Moreover, it is well documented that abnormal D-dimer is helpful in indicating deep venous thrombosis in cardiovascular diseases. Thus, we analysed the correlation between D-dimer level with clinical prognosis in patients with and without cardiovascular disease. First, there was a difference in D-dimer levels of patients with and without cardiovascular disease in the poor group (P = 0.047; Table SIII). Among patients with cardiovascular disease in the poor group, no difference was observed between non-survivors and survivors (P = 0.83). Last, among patients without cardiovascular disease in the poor group, non-survivors had higher D-dimer levels than survivors (P = 0.02).

As for the current therapeutic regimens for COVID-19, no effective antivirals and vaccines have yet been recommended for patients with COVID-19. A previous report claimed that a D-dimer level >1 μg/ml was associated with a lower mortality after heparin treatment. Thus, anticoagulant treatment appears to be beneficial in severe COVID-19 cases. Given that non-survivors had higher D-dimer levels than survivors among the patients without cardiovascular disease in the poor group, timely and effective anticoagulant treatment may be workable.

When administering anticoagulant treatment, proper attention should be paid to diffuse alveolar haemorrhage (DAH), which is a life-threatening complication after warfarin use. Thus, international normalized ratio (INR) should be used for early diagnosis and rapid therapeutic intervention.

Overall, dynamical changes of D-dimer level are positively correlated with the prognosis of COVID-19. Anticoagulant treatment may benefit severe COVID-19 patients, especially those without cardiovascular disease.

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Author contributions
YL, KZ, HW, WC, ZP, YL and XY 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. Concept and design: YL, ZP, YL and XY. Acquisition, analysis, or interpretation of data: all authors. Drafting of the manuscript: YL, ZP, YL and XY. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: YL, KZ, HW, WC, ZP, YL and XY. Supervision: YL and XY. Drs YL, KZ, HW, and WC contributed equally to this work.

Conflicts of interest
The authors declare that they have no conflicts of interest.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Odds ratio of prognosis associated with 1 μg/ml increment in D-dimer level on admission.

Table SII. Odds ratio of prognosis associated with 1 μg/ml increment in D-dimer level.

Table SIII. Differences in D-dimer level among patients with and without cardiovascular disease and survivors and non-survivors with cardiovascular disease in the poor group.

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Reflection on passive immunotherapy in those who need most: some novel strategic arguments for obtaining safer therapeutic plasma or autologous antibodies from recovered COVID-19 infected patients

The COVID-19 pandemic is an emerging new human disease, for which no vaccines, or monoclonal antibodies (mAbs) or drugs, are currently available for therapy. Active vaccination requires the induction of an immune response against a given agent in a susceptible individual for the purpose of preventing or treating an infectious disease and this usually takes time to develop. Thus, the use of existing autologous Ab administration, obtainable from recovered COVID-19 patients two weeks after recovery, is the best and the most practical strategy for providing immediate passive immunity to susceptible recipients in need. Recently, the use of convalescent blood-derived products was proposed by one of the authors of this paper (JS) as an early option for treating patients with Ebola virus disease.2,3 Therefore, human convalescent plasma, obtainable by plasmapheresis of plasma or immunoglobulin-containing fractions donated by volunteers recovered from a COVID-19 attack, has been proposed and implemented with success in COVID-19 cases.2–6 Specific requirements and standards for preparation, qualification, storage and distribution of these blood preparations need to be fully explored. Administration of volumes ranging from 200 to 600 ml of immune plasma (8–10 ml/kg) once per day and for up to 3–7 consecutive days is generally recommended to be safe. However, some technical issues still need to be solved such as the optimal threshold for the serum titer of specific neutralizing antibodies [≥160 or ≥320 by the enzyme immunoassay (EIA) method] in the preparation and the real utility of performing a pathogen (viral) inactivation treatment of such products. In fact, critically ill COVID-19 patients as well as those in early phases of the disease might be excellent candidates for passive immunotherapy, and for further randomized clinical trials for addressing its clinical usefulness in various patient subcategories. The immunocompromised status associated with haematological malignancies may enhance the risk of COVID-19 infections. Based on this consideration, it might be postulated that either the preventive or the therapeutic use of convalescent plasma may be beneficial in chemotherapy-treated cancer patients, possibly mitigating the impact of COVID-19.7 However, the incidence and potential predictive parameters of mortality of COVID-19 in patients with haematological malignancies is still matter of investigation.5 Moreover, gene response, and