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Original Article

Clinical and laboratory predictors for disease progression in patients with COVID-19: A multi-center cohort study

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Abstract

Background: Reliable clinical and laboratory predictors of coronavirus disease 2019 (COVID-19) disease progression could help to identify the subset of patients who are susceptible to severe symptoms. This study sought to identify the predictors for disease progression in patients with COVID-19.

Methods: This study recruited consecutive patients from four hospitals between March 1, 2020, and July 31, 2021. Demographic characteristics, laboratory results, and clinical outcomes were collected.

Results: Among the 239 enrolled patients, 39.3% (94/239) experienced in-hospital disease progression. Multivariate logistic regression revealed that coronary arterial disease (CAD)
At a glance commentary

Scientific background on the subject

A subgroup of coronavirus disease 2019 (COVID-19) patients with mild-to-moderate symptoms may develop disease progression and become critically ill. Identifying the predictors for disease progression in COVID-19 patients may help in early targeting patients who require aggressive medical intervention.

What this study adds to the field

Independent predictors for disease progression include underlying comorbidity with CAD and CVA, decreased platelet count, and increased CRP. Patients susceptible to disease progression presented persistently low lymphocyte counts and elevated CRP levels. COVID-19 disease progression in severe/critical patients may be mediated by a persistent inflammatory response. A sustained elevated viral load may play a role in mediating disease progression in patients with mild/moderate severity.

Background

The emergence of coronavirus disease 2019 (COVID-19) has had a considerable impact on public health globally. As of January 26, 2022, there have been more than 356 million confirmed COVID-19 cases worldwide with more than 5.6 million deaths attributed to the pandemic (https://covid19.who.int/). COVID-19, the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has clinical manifestations ranging from a complete lack of symptoms to respiratory failure [1,2]. A number of studies have reported that some underlying diseases affect the prevalence and outcomes of COVID-19, such as cardiovascular disease, pneumonia, depression, diabetes, atrial fibrillation, chronic obstructive pulmonary disease (COPD), and hypertension as well as high cytokine, lactate dehydrogenase (LDH), and C-reactive protein (CRP) levels [3,4].

Roughly 80% of COVID-19 patients develop mild/moderate symptoms requiring minimal medical intervention; however, the other 20% suffer a more severe form of the disease, requiring hospitalization, ventilation, and/or intensive care unit (ICU) admission [1,2]. This has prompted considerable research into the pathogenesis of COVID-19 as well as the risk factors for adverse clinical outcomes. Most articles pertaining to COVID-19 have focused on severe patients or composite end-points, including the use of mechanical ventilation, admission to the ICU, or death [5,6]. The fact that a subgroup of patients with mild-to-moderate symptoms become critically ill necessitates research into the progression of COVID-19 as the primary outcome, rather than as a composite end-point [7,8]. It is very likely that this avenue of inquiry could lead to important insights by which to identify patients facing an elevated risk of disease progression and thus requiring aggressive medical intervention [7,9]. Note that this is essential for the early management of such patients in terms of improving outcomes and ensuring the optimal use of available medical resources.

Previous research has shown that inflammation and direct viral damage are essential mechanisms contributing to COVID-19 severity [10]. Questions pertaining to the role of elevated proinflammatory cytokine levels in serum in the pathogenesis and progression of COVID-19 have prompted numerous researchers to investigate the role of inflammatory markers in predicting the disease severity of COVID-19 [11]. Overall, researchers have linked higher levels of inflammatory markers (e.g., CRP and lymphocyte count) as well as various inflammatory cytokines and chemokines to the severe clinical course [12]. Unfortunately, cytokine/chemokine analysis is generally too expensive for routine situations, and the results of cytokine/chemokine measurements are not always available in a timely manner. The ability to use widely available hematological and biochemical parameters as surrogate markers of disease progression could potentially have high prognostic value. In the current study, we sought to identify the predictors for disease progression in COVID-19 patients. We also compared serial changes in laboratory parameters and viral load in patients with or without disease progression.

Materials and methods

Study population

This paper reports on a multi-center, retrospective, observational study of subjects hospitalized due to COVID-19 and managed within the Chang Gung Health System. We recruited consecutive patients from four hospitals, including two large tertiary care centers and two community hospitals. Subjects
were included if they were >18 years old and had a laboratory-confirmed diagnosis of COVID-19 via polymerase chain reaction (PCR) testing. Data were collected for 239 consecutive patients admitted to the Chang Gung Health System between March 1, 2020, and July 31, 2021. The study was approved by the Institutional Review Board of the Chang Gung Memorial Foundation (IRB No. 20210071280). Informed consent was waived due to the retrospective nature of this study. All data were collected from electronic medical records. Patients who had available laboratory data within 24 h of admission were collected. The first time point (day 0) was their baseline concentration within 24 h of admission.

Data collection

Medical information including baseline characteristics, comorbidities, as well as clinical, laboratory, treatment, and outcome data were extracted using data collection forms, which were checked independently by two trained physicians.

Definitions

All of the patients included in the study were diagnosed with COVID-19 in accordance with the Interim Guidelines for Clinical Management of SARS-CoV-2 Infection (11th edition) released by the Taiwan Centers for Disease Control (CDC) [13]. The patients were accordingly classified as follows: (1) mild cases involving mild clinical symptoms without pneumonia manifestation in imaging; (2) moderate cases involving fever and respiratory tract symptoms as well as pneumonia manifestation in imaging; (3) severe cases involving any of the following: (i) respiratory distress with respiratory rates ≥30 breaths/minute; (ii) oxygen saturation of <94% in resting state; (iii) arterial oxygen tension (PaO2) over inspiratory oxygen fraction (FiO2) ratio of <300 mmHg (1 mmHg = 0.133 kPa); and (iv) multiple pulmonary lobes with images showing progression in more than 50% of lesions within 24–48 h; and (4) critically ill cases involving the following: (i) respiratory failure requiring mechanical ventilation; (ii) shock; and (iii) multiple organ failure requiring monitoring and treatment in the ICU. Progression was defined as an increase in severity. Unchanged severity throughout the observation period was not classified as progression. AKI events were defined as any of the following criteria occurring within 7 days after admission: An increase in serum creatinine level of ≥0.3 mg/dL within a period of 48 h or an increase in serum creatinine level of ≥1.5 times from baseline within a period of 7 days. Note that both of these criteria were suggested in the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Acute Kidney Injury (AKI) [14]. Cardiac injury was defined by at least one documented assay indicating elevated high sensitivity troponin-I [15].

COVID-19 management protocol

The strategies used in the management of COVID-19 were fairly homogenous across the four hospitals, all of which adopted protocols in line with the Interim Guidelines for Clinical Management of SARS-CoV-2 Infection [13]. This involved regularly monitoring vital signs and oxygen saturation (severe cases were monitored continuously), strengthening supportive treatment, providing sufficient calories, and maintaining the stability of the internal environment (e.g., water, electrolytes, and acid–base balance). Supplemental oxygen therapy was immediately administered to patients upon hypoxemia presentation. The target oxygen saturation was a pulse oxygen saturation of ≥90%. In the event that standard oxygen therapy failed, then high-flow nasal catheter oxygen or non-invasive ventilation was used. If non-invasive mechanical ventilation failed to provide benefits, then invasive mechanical ventilation was initiated. Antiviral therapy and anti-inflammatory agents were administered in accordance with standardized guidelines. Remdesivir was administered to patients with SPO2 ≤ 94% under room air or supplied oxygen. Low dose dexamethasone (6 mg per day for no more than 10 days) was administered to patients with SPO2 ≤ 94% under room air or supplied oxygen, those presenting respiratory failure, and those requiring extracorporeal membrane oxygenation (ECMO). Tocilizumab was administered to patients with SPO2 < 94% under room air or supplied oxygen as well as those presenting respiratory failure or requiring ECMO. Antimicrobial agents (oral or intravenous) were prescribed in accordance with the condition of the patient. Note that all medical expenses were reimbursed by the National Health Insurance in Taiwan. Anti-viral and anti-inflammatory agents were provided by the Taiwan CDC in accordance with standard guidelines. Therefore, the medical interventions among the 4 hospitals were highly homogenous and maintained consistency with the standard guidelines.

Laboratory data

All blood samples were obtained and analyzed using standardized laboratory methods. Routine hematological and biochemical testing included white blood cell count (WBC) (normal range 3900–10,600, 1000/μL), lymphocyte count (normal range 780–5,936, 1000/μL), prothrombin time (PT) (normal range 8–12, seconds), activated partial prothrombin time (aPTT) (normal range 24.6–33.8, seconds), C-reactive protein (CRP) (normal range <5 mg/L), D-dimer (<0.55 mg/L), lactate dehydrogenase (LDH) (normal range 135–225, U/L), ferritin (normal range 13–150, ng/mL), interleukin-6 (normal range <7 pg/mL), blood urea nitrogen (BUN) (normal range 6–21, mg/dL), creatinine (normal range 0.44–1.27, mg/dL), total bilirubin (normal range 0.2–1.4, mg/dL), aspartate aminotransferase (AST) (normal range <34 U/L), and alanine aminotransferase (ALT) (normal range <36 U/L). The PCR cycle threshold (Ct) values of nasopharyngeal samples were measured on day 1 and 10 after hospitalization.

Statistical analysis

All data were expressed as medians with interquartile range (IQR), mean ± standard error of the mean (SEM), or percentage, unless otherwise indicated. The Student’s t-test was used to compare the means of continuous variables and normally distributed data; otherwise, the Mann–Whitney test was used. Categorical variables were tested using the Chi-square test or Fisher’s exact test. Univariate analysis was first performed to identify the predictors for disease progression. All variables
with a p value of <0.1 in univariate regression analysis were entered into a forward logistic regression model to identify factors independently predictive of disease progression. A p value of <0.05 using a two-sided test was considered statistically significant. All statistical analysis was performed using SPSS software, version 20.0 (SPSS, Inc., Chicago, IL).

**Results**

**Demographics and laboratory, treatment, and prognosis characteristics**

A total of 239 PCR-confirmed cases of COVID-19 were recruited (Table 1). Among this cohort, 39.3% (94/239) experienced in-hospital disease progression and 60.7% (145/239) did not progress in-hospital. Among the 4 hospitals, 2 tertiary hospitals recruited 175 patients and the other 2 community hospitals recruited 64 patients. There were 66 patients and 28 patients experienced disease progression in tertiary and community hospitals, respectively. The incidences of disease progression were similar between patients recruited from 2 different classes of hospitals (37.7% vs. 43.8%; p = 0.398). The incidence of disease progression among COVID patients was based on their condition at the time of admission, as follows: Mild cases (16.1% (9/56)), moderate cases (41.9% (18/43)), severe cases (33.0% (33/100)), and critical cases (85.0% (34/40)). Basic clinical information is listed in Table 1. The median patient age was 62 years (IQR: 48–71 years), and 51% of patients were male (122/239). Compared to individuals without disease progression, those with disease progression were significantly older and more likely to have comorbidities. The median (IQR) time from admission to disease progression was 6 (5.0–9.0) days. Patients with disease progression presented lower lymphocyte and platelet counts as well as higher CRP, LDH, ferritin, and IL-6 levels (Table S1). The values of aPTT were higher in patients with disease progression than in those without progression.

Table 2 lists treatments and outcomes. Dexamethasone, tocilizumab, and anti-viral agents (e.g., Remdesivir) were administered for mild, moderate, and severe cases. Patients with disease progression were more likely to use tocilizumab and antiviral agents. The mortality rate in the total cohort was 6.8% (16/239), with 6.6% (6/94) and 7.2% (8/115) in patients with and without disease progression, respectively. The median time from admission to death was 7 days (IQR: 5–14 days).

### Table 1 Baseline characteristics of COVID-19 patients.

|                         | Total cohort n = 239 | Disease progression n = 94 | No disease progression n = 145 | p value |
|-------------------------|----------------------|-----------------------------|-------------------------------|---------|
| **Age, yr**             | 62 (48–71)           | 69 (60.8–78.1)              | 57 (41–61)                    | <0.0001 |
| **Male gender**         | 122 (51.0%)          | 49 (52.1%)                  | 73 (50.5%)                    | 0.788   |
| **BMI**                 | 24.2 (21.5–27.1)     | 24.6 (22.3–26.5)            | 24.1 (21.1–27.6)              | 0.721   |
| **Active smoker**       | 11 (4.6%)            | 4 (4.3%)                    | 7 (4.8%)                      | 0.837   |
| **Severe/critical severity** | 140 (58.6%)          | 67 (71.3%)                  | 73 (50.3%)                    | 0.001   |
| **Comorbidities**       |                      |                             |                               |         |
| Hypertension            | 89 (27.2%)           | 47 (50.0%)                  | 42 (29.0%)                    | 0.001   |
| CAD                     | 35 (14.6%)           | 25 (26.6%)                  | 10 (6.9%)                     | <0.0001 |
| Heart failure           | 10 (4.2%)            | 5 (5.3%)                    | 5 (3.4%)                      | 0.480   |
| Af                      | 10 (4.2%)            | 6 (6.4%)                    | 4 (2.8%)                      | 0.172   |
| CVA                     | 12 (5.0%)            | 11 (11.7%)                  | 1 (0.7%)                      | <0.0001 |
| DM                      | 48 (20.1%)           | 24 (25.5%)                  | 24 (16.6%)                    | 0.091   |
| CKD                     | 21 (8.8%)            | 13 (13.8%)                  | 8 (5.5%)                      | 0.027   |
| COPD                    | 11 (4.6%)            | 7 (7.4%)                    | 4 (2.8%)                      | 0.091   |
| Asthma                  | 7 (2.9%)             | 5 (5.3%)                    | 2 (1.4%)                      | 0.078   |
| Autoimmune disease      | 3 (1.3%)             | 1 (1.1%)                    | 2 (1.4%)                      | 0.831   |
| Malignancy              | 9 (3.8%)             | 4 (4.3%)                    | 5 (3.4%)                      | 0.749   |
| **Laboratory findings** |                      |                             |                               |         |
| WBC, 1000/μL            | 5550 (4600–7725)     | 6150 (4850–9000)            | 5250 (4300–6675)              | 0.556   |
| Lymphocyte count, 1000/μL | 970 (640–1390)       | 797.6 (516.4–1185.3)        | 1151.5 (758.0–1579.6)         | 0.001   |
| Platelet, 1000/μL       | 196 (155–249)        | 171 (145.5–220)             | 217 (172.5–277.5)             | <0.0001 |
| PT, seconds             | 12 (11.2–12.8)       | 12 (11.1–12.9)              | 12 (11.2–12.6)                | 0.430   |
| aPTT, second            | 29.3 (27.4–31.4)     | 29.9 (27–32)                | 28.8 (27.4–28.8)              | 0.039   |
| D-dimer, mg/L           | 764 (426–2000)       | 620 (389.5–1318)            | 428 (278–759.5)               | 0.900   |
| BUN, mg/dL              | 13.7 (10.1–20.1)     | 16.1 (12.7–23.4)            | 12.3 (8.4–16.5)               | 0.478   |
| Creatinine, mg/dL       | 0.82 (0.64–1.08)     | 0.84 (0.74–1.17)            | 0.78 (0.6–1.01)               | 0.559   |
| AST, U/L                | 32 (23–45)           | 36 (27–50)                  | 29.3 (21–42)                  | 0.147   |
| ALT, U/L                | 28 (19–41)           | 29 (23.3–41.8)              | 26 (18–41)                    | 0.680   |
| Total bilirubin, mg/dL  | 0.4 (0.3–0.6)        | 0.4 (0.3–0.7)               | 0.5 (0.3–0.6)                 | 0.994   |
| LDH, U/L                | 321 (227–442)        | 398 (247.5–499.5)           | 315.5 (221–409)               | 0.025   |
| CRP, mg/L               | 28.6 (6.9–81.2)      | 57.2 (16.3–100.9)           | 18.9 (3.1–52.8)               | <0.0001 |
| Ferritin, ng/ml         | 620 (286.1–1035.5)   | 785 (372.5–1321.3)          | 526 (246–828)                 | 0.017   |
| Interleukine-6, pg/mL   | 25.9 (10.1–69.0)     | 46.7 (20.2–93.4)            | 14.9 (6.3–32.3)               | 0.041   |

Data are expressed as n (%) and median (IQR).

Abbreviations: COVID-19: coronavirus disease 2019; BMI: body mass index; CAD: coronary arterial disease; Af: atrial fibrillation; CVA: cerebrovascular accident; DM: diabetes mellitus; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; WBC: white blood cell; PT: prothrombin time; aPTT: activated partial prothrombin time; BUN: blood urine nitrogen; AST: Aspartate Transaminase; ALT: alanine transaminase; LDH: lactate dehydrogenase; CRP: C-reactive protein.
more commonly used for patients with disease progression than for those without. Acute kidney injury, cardiac injury, respiratory failure, and ARDS were more common in individuals with disease progression than in those without. Patients with disease progression were more likely to die than were those without disease progression. Patients with disease progression also experienced longer hospital stays and a longer viral conversion to PCR Ct value > 30.

**Multivariate logistic regression analysis of factors associated with disease progression**

Univariate and multivariate logistic regression analyses were used to determine the independent effects of clinical and laboratory variables (Table 3). Univariate analysis (cutoff p-value of 0.1) identified the following factors: age > median value (62 years old), hypertension, CAD, CVA, DM, CKD, severe/critical severity, lymphocyte count < median value (5550 x 1000/µL), platelet count < median value (196 x 1000/µL), aPTT > median value (29.3 s), LDH > median value (321 U/L), CRP > median value (28.6 mg/L), ferritin > median value (620 ng/mL), and IL-6 > median value (25.9 pg/mL). Multivariate logistic regression analysis identified the following factors: CAD (OR, 4.15; 95% C.I., 1.47–11.66), CVA (OR, 12.98; 95% C.I., 1.30–129.51), platelet count < median value (OR, 3.23; 95% C.I., 1.65–6.32), and CRP > median value of (OR, 2.25; 95% C.I., 1.02–4.99).

**Longitudinal changes in laboratory parameters among COVID-19 patients**

We investigated the links between disease progression and serial changes in longitudinal WBC, platelet count, D-dimer, LDH, CRP, and ferritin levels. Note that this analysis was limited to the subgroup of patients for whom this laboratory data was available. We collected data pertaining to these variables at days 0, 4, and 7. Compared to patients without disease progression, those with disease progression presented significantly low lymphocyte counts and elevated LDH, CRP, and ferritin levels. Note however that during the first week of hospitalization, LDH and ferritin levels were significantly higher among patients with disease progression than among those without. Patients with disease progression was consistently lower among COVID-19 patients of mild/moderate severity. Day-0 LDH and ferritin levels were significantly higher among patients with disease progression than among those without. Note however that during the first week of hospitalization, none of the variables were persistently different between patients with and without progression. Table S2 lists laboratory results at three time points in patients of mild/moderate severity with and without disease progression.
Fig. 3 plots serial changes in the laboratory variables of COVID-19 patients with severe and critical severity. The day-0 lymphocyte count of patients with disease progression was significantly lower and WBC as well as CRP levels were significantly higher than those of patients without progression (Fig. 3). The lymphocyte count of patients with disease progression was persistently lower and CRP levels were significantly higher than those of patients without progression (at all three time points). Table S3 lists the laboratory results for patients of mild/moderate severity with or without disease progression (at all three time points).

**Analysis of PCR Ct values**

Based on a comparison of viral shedding patterns, positive PCR tests with Ct ≤30 (as a surrogate indicator of viral load)
were significantly longer in patients with disease progression than in those without (Table 2). On days 1 and 10, the Ct values of patients with disease progression were significantly lower than that of patients without progression (Fig. 4A). On days 1 and 10, the Ct values of patients of mild/moderate severity were lower among patients with disease progression than in

Fig. 2 Relationship between serial laboratory parameters and disease progression in COVID-19 patients of mild/moderate severity. White blood cell (WBC) count (A), lymphocyte count (B), D-dimer (C), LDH (D), CRP (E), and ferritin (F) in patients with (+, red circle) or without (–, blue circle) disease progression were measured on days 0, 4, and 7. *p < 0.05 indicates a significant difference between patients with or without disease progression on the same day. Data are expressed as mean ± SEM.

Fig. 3 Relationship between serial laboratory parameters and disease progression in severe/critical COVID-19 patients. White blood cell (WBC) count (A), lymphocyte count (B), D-dimer (C), LDH (D), CRP (E), and ferritin (F) in patients with (+, red circle) or without (–, blue circle) disease progression were measured on days 0, 4, and 7. *p < 0.05 indicates difference between patients with or without disease progression on the same day. Data are expressed as mean ± SEM.

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those without progression (Fig. 4B). Severe and critical patients (with and without disease progression) did not differ significantly in terms of Ct values at day 1 and 10. Table S3 lists the Ct values for the entire cohort and subgroups of COVID-19 patients with or without disease progression.

Factors associated with disease progression

The independent predictors for disease progression in patients with different initial illness severities were also determined. In patients with initial mild/moderate severities (Table S4), platelet count < median value (OR, 12.72; 95% C.I., 2.40–67.54), and CRP > median value (OR, 4.65; 95% C.I., 1.03–20.92) were independent predictors for disease progression. In patients with severe/critical severities (Table S5), WBC count > median value (OR, 3.20; 95% C.I., 1.36–7.53), platelet count < median value (OR, 2.91; 95% C.I., 1.24–6.80), and CRP > median value (OR, 2.22; 95% C.I., 1.01–4.86) were independent predictors for disease progression.

The baseline characteristics between patients with mild/moderate and severe/critical severities were listed (Table S6). Multivariate analysis showed that age (OR, 1.11; 95% C.I., 1.04–1.19; p = 0.001) and elevated LDH levels (OR, 1.01; 95% C.I., 1.01–1.02; p = 0.003) were independent factors associated with severe and critical severities in COVID-19 patients (Table S7). The factors associated with initial disease severity are different from factors associated with disease progression.

The clinical information and laboratory values between patients with rapid (progression period within 3 days) and slow disease progression (progression period longer than 3 days) were listed (Table S8). The length of disease progression was unaffected by age and initial COVID-19 severity. Compared with patients with rapid disease progression, patients with late progression had higher incidence of hypertension (p = 0.044), CRP levels (p = 0.036), and longer prothrombin time (p = 0.018).

Discussion

The study revealed a high incidence of disease progression among hospitalized COVID-19 patients. Furthermore, we determined that patients with disease progression were associated with worse clinical outcomes. Patients with disease progression were more likely to present comorbidities, decreased lymphocyte and platelet counts, and increased expression of inflammatory markers. Independent predictors for disease progression included the following: underlying comorbidity with CAD and CVA, low platelet count, and elevated CRP. Disease progression was associated with persistently low lymphocyte counts, higher CRP levels, and higher viral load.

Evidence suggests that platelet count is independently associated with disease severity and the risk of mortality in ICUs [16]. A low platelet count has previously been linked with an increased risk of severe disease and mortality in COVID-19 cases, which means that it could serve as a predictor of disease exacerbation during hospitalization [17]. Damaged lung tissue and pulmonary endothelial cells can activate platelets in the lungs, resulting in the aggregation and formation of microthrombi leading to increased platelet consumption [18]. Serum CRP is one of the most important acute phase reactants, which usually increases rapidly after the onset of inflammation, cell damage, or tissue injury. Most pulmonary diseases characterized by features of inflammation raise circulating CRP levels in response to inflammatory cytokines, such as IL-6, IL-1, and TNF-α [19]. Direct attacks from SARS-CoV-2 and organ damage caused by an excessive inflammatory response may be responsible for the pathogenesis of COVID-19 disease progression [20]. Thus, markedly elevated serum CRP levels in patients with COVID-19 may be an indication of excessive inflammatory stress, which could contribute to disease progression and poor clinical outcomes [21].

SARS-CoV-2 infection often results in multiple organ injury accompanied by an expression of serum inflammatory mediators, indicating that COVID-19 is a systemic inflammatory illness rather than just a lung disease [22]. Longitudinal analysis of the correlation between serum inflammatory parameters and disease progression in patients as a function of disease severity may extend our understanding of the role of the host immune system in the pathogenesis and progression of COVID-19. In severe/critical patients without disease progression, medical intervention generally results in a gradual

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increase in CRP levels and a decrease in lymphocyte count. Severe/critical patients with disease progression often present sustained high CRP levels and persistent lymphopenia throughout the course of the disease. In patients of mild/moderate severity with and without disease progression, we observed no sustained change in any of these biomarkers throughout the study period. The serial measurement of viral load (as indicated by Ct value on days 1 and 10) demonstrated a similar viral load in patients with or without disease progression, particularly in severe/critical patients. Among patients of mild/moderate severity, those with disease progression presented persistently higher viral load, compared with those without progression. Taken together, it appears that the progression of COVID-19 in severe/critical patients could perhaps be mediated by a persistent inflammatory response, whereas sustained elevated viral load may play a role in mediating disease progression in patients of mild/moderate severity. We conclude that viral load and a systemic inflammatory response may play a distinct role in mediating disease progression for patients, regardless of illness severity.

There is a pressing need for reliable biomarkers related to COVID-19 disease progression by which to stratify high-risk patients. The rapid spread of disease necessitates the immediate categorization of patients to ensure optimal resource allocation. The study demonstrated that patients presenting comorbidity with CAD and CVA, increased levels of CRP, and/or a decreased platelet count are strong candidates for disease progression and should therefore be given priority in the allocation of resources. The incorporation of these variables within clinical and laboratory algorithms could perhaps be used for future research. The association of comorbidities and low platelet count, and CRP levels [23] have been reported in different studies. However, the present study further investigated the role of these biomarkers in different initial COVID-19 severities. Attention may be focused on COVID-19 patients with different initial severity and close monitor should be applied to those with high risk for disease progression.

According to the report from whole genome sequencing by Taiwan CDC, the recruited subjects of this study were infected by wild type, alpha, and delta strains of SARS-CoV-2. However, omicron variant is currently predominant strain for SARS-CoV-2 infection in the world. A retrospective case control study reported that higher LDH and CRP levels were associated with pneumonia in patients infected by omicron variant [24]. The percentage of patients with pneumonia, who required oxygen, and who required hospitalization was significantly lower in the omicron group than in the delta group. When adjusted with matched age and comorbidity, omicron variant induced lower CRP and LDH level in COVID-19 patients compared with patients infected by delta variant. Further large-scare study is mandatory to compare the difference of disease progression predictor among these strains.

One major limitation of the current study is its retrospective nature, which may have led to bias in the selection of study subjects. Moreover, the sample size was small, such that the results should be interpreted with caution. Note also that all confirmed cases in Taiwan were admitted to hospital for treatment, based on guidelines promulgated by the Taiwan CDC. This made it possible for us to longitudinally follow up patients and maintain consistency among hospitals in terms of treatment regimens. Due to regional shortage of COVID-19 vaccine during that outbreak of pandemic, most of the recruited patients were unvaccinated. Therefore, use of these results in vaccinated COVID-19 patients should be applied with caution.

In conclusion, the study revealed that comorbidity with CAD and CVA, decreased platelet count, and increased CRP levels were independently associated with disease progression in hospitalized COVID-19 patients. Our results also suggest that these markers could be used at the time of admission as predictors of disease progression in order to identify patients requiring intensive monitoring and a more aggressive approach to therapy.

Conflicts of interest

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bj.2022.11.002.

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