Decreased Eosinophil Counts and Elevated Lactate Dehydrogenase Predict Severe COVID-19 Patients with Underlying Chronic Airway Diseases

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Research

Keywords: Eosinopenia, Predictor, Chronic airway inflammation, COVID-19

Posted Date: August 10th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-53471/v1

Abstract

Background: Several predictors for the severity of coronavirus disease 2019 (COVID-19) have been reported, including decreased circulating lymphocytes and eosinophil counts. However, chronic airway inflammation characterized by accumulated lymphocytes or eosinophils may affect the pathogenesis of COVID-19. We aimed to investigate the predictors for the severity of COVID-19 in patients with chronic airway diseases.

Methods: In this retrospective cohort study, we reviewed medical records of all laboratory-confirmed COVID-19 patients with chronic bronchitis, chronic obstructive pulmonary disease (COPD) and asthma admitted in Sino-French New City Branch of Tongji Hospital, a large regional hospital in Wuhan, China, from January 26th to April 3rd. The Tongji Hospital ethics committee approved this study.

Results: There were 59 patients with underlying chronic airway inflammation including chronic bronchitis, COPD, and asthma. When compared with non-severe patients, severe patients were more likely to have decreased lymphocyte counts (0.6 vs. 1.1× 10⁹/L, $p < 0.001$), eosinopenia (< 0.02 × 10⁹/L, 73% vs. 24%, $p < 0.001$), increased lactate dehydrogenase (LDH) (471.0 vs. 230.0 U/L, $p < 0.001$) and elevated IL-6 level (47.4 vs. 5.7 pg/ml, $p = 0.002$) on admission. Eosinopenia and elevated LDH were significantly associated with disease severity in both univariate and multivariate regression models included the above variables. Eosinopenia was also an independent risk factor for mortality of this cohort in a multivariate model included the above variables. Moreover, eosinophil counts and LDH levels tended to return to normal range over time in both groups after treatment and severe patients recovered slower than non-severe patients, especially eosinophil counts.

Conclusions: Eosinopenia and elevated LDH are potential predictors of disease severity in COVID-19 patients with underlying chronic airway diseases. Theses predictors may help clinicians identify the severe COVID-19 patients with chronic bronchitis, COPD, and asthma.

Introduction

In December 2019, coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) occurred in Wuhan, Hubei Province, China. As of July 20, 2020, 14 348 858 of COVID-19 confirmed cases and 603 691 deaths were reported in over 215 countries worldwide [1], demanding an urgent need for early identification for severe cases. The SARS-CoV-2 virus, which belongs to the betacoronavirus, is highly homologic (with 88% identity) to two bat-derived SARS-like coronaviruses, while more distant from SARS-CoV (around 79%) and Middle East respiratory syndrome coronavirus (MERS-CoV, around 50%) [2]. Clinical evidence has suggested that SARS-CoV can be transmitted from person to person via direct contact or through droplets from infected individuals [3, 4]. SARS-CoV-2 is able to attack the respiratory system through binding the cell entry receptors angiotensin-converting enzyme 2 (ACE2) on airway epithelial cells and results in pneumonia and respiratory failure in critically ill patients.

Chronic bronchitis, chronic obstructive pulmonary disease (COPD), and asthma are common respiratory diseases with chronic airway inflammation [5–9]. Eosinophils, neutrophils, and macrophages in innate immune response significantly increase in the airway and lung during the initial phase of inflammation. Subsequently, activated adaptive immunity leads to the recruitment of T and B lymphocytes. Th1, Th2, and Th17 cells play a crucial role in COPD, asthma, and chronic bronchitis, resulting in mucus overproduction and airflow obstruction [5, 8]. Lymphocytopenia, however, has been reported in several studies in severe patients infected with SARS-CoV-2 [10–12]. Recently, circulating eosinophil counts were also reported to be decreased in COVID-19 patients, and associated with the severity of the disease [13, 14]. Therefore, patients with underlying COPD, asthma, and chronic bronchitis may have different inflammatory states after SARS-CoV-2 infection compared to patients without chronic airway inflammation. [10–12, 15–17]. In this study, we aimed to identify the potential predictors for the disease severity of COVID-19 patients with underlying chronic airway diseases including chronic bronchitis, COPD, and asthma.

In this retrospective cohort study, we reviewed medical records of 59 laboratory-confirmed COVID-19 patients with underlying chronic airway inflammation and compared the demographic, clinical, and radiological characteristics as well as laboratory results between severe and non-severe patients in this cohort. Potential predictors of disease severity were identified in the abnormal laboratory findings using univariate and multivariate regression models.

Results

Demographics and clinical characteristics of non-severe and severe COVID-19 patients with chronic airway diseases

A total of 1888 patients were admitted. Fifty-nine patients with underlying chronic airway inflammation, including COPD (0.95%), asthma (0.53%), and chronic bronchitis (1.64%) were confirmed to have SARS-CoV-2 infection. Thirty-three patients were classified as non-severe patients and twenty-six patients were classified as severe patients. Although COPD was more common in severe COVID-19 patients when compared with non-severe COVID-19 patients (42% vs. 21%), the difference was not statistically significant.

The median age for all patients was 71 years (interquartile range, 57–80) and more than half of them (54%) were over 70 years old. The majority (71%) of patients were male (Table 1). There was no significant difference in age and sex between non-severe and severe patients. Thirty-one (53%) patients had one or more comorbidities besides the three chronic airway diseases, with cardiovascular disease (46%) and endocrine system disease (15%) being the most common comorbidity. There were no significant differences in the presence of these comorbidities between the non-severe and severe COVID-19 patients. Half of the patients had smoking histories or current smokers.

Table 1
Demographics and clinical characteristics of COVID-19 patients with chronic airway inflammation on admission.

	All patients (n = 59)	Non-severe patients (n = 33)	Severe patients (n = 26)	p value
Age	71 (57–80)	70 (55–79)	74 (64–82)	0.184
< 30yr	2 (3%)	1 (3%)	1 (4%)	0.726
30-49yr	5 (8%)	4 (12%)	1 (4%)	
50-69yr	20 (34%)	11 (33%)	9 (35%)	
≥ 70 year	32 (54%)	17 (52%)	15 (58%)	
Sex				
Female	17 (29%)	10 (30%)	7 (27%)	0.776
Male	42 (71%)	23 (70%)	19 (73%)	
Comorbidity	31 (53%)	17 (52%)	14 (54%)	0.859
COPD	18 (30%)	7 (21%)	11 (42%)	0.081
Chronic bronchitis	31 (53%)	18 (55%)	13 (50%)	0.728
Asthma	10 (17%)	8 (24%)	2 (8%)	0.093
Cardiovascular Disease	27 (46%)	14 (42%)	13 (50%)	0.562
Cerebrovascular Disease	3 (5%)	1 (3%)	2 (8%)	0.418
Digestive system Disease	1 (2%)	0 (0%)	1 (4%)	0.441
Endocrine system Disease	9 (15%)	4 (12%)	5 (19%)	0.451
Nephrosis	2 (3%)	1 (3%)	1 (4%)	0.863
Urinary system Disease	1 (2%)	1 (3%)	0 (0%)	1.000
Viral hepatitis	1 (2%)	1 (3%)	0 (0%)	1.000
Smokers	29 (49%)	14 (42%)	15 (58%)	0.244
Symptoms and signs				

Data are median (IQR), n (%), or n/N (%), where N is the total number of patients with available data. p values comparing severe with non-severe patients were calculated by $\chi 2$ test, Fisher's exact test, or Mann-Whitney U test, as appropriate. COVID-19, coronavirus disease 2019.

	All patients (n = 59)	Non-severe patients (n = 33)	Severe patients (n = 26)	p value
Fever				
< 38.5℃	21 (36%)	13 (39%)	8 (31%)	0.407
≥ 38.5℃	28 (47%)	14 (42%)	14 (54%)	
Cough	43 (73%)	21 (64%)	22 (85%)	0.072
Chest tightness	16 (27%)	7 (21%)	9 (35%)	0.250
Hemoptysis	1 (2%)	0 (0%)	1 (4%)	0.441
Dyspnea	25 (42%)	8 (24%)	17 (65%)	0.001
Fatigue	28 (47%)	15 (45%)	13 (50%)	0.728
Myalgia	11 (19%)	7 (21%)	4 (15%)	0.568
Nausea	2 (3%)	1 (3%)	1 (4%)	0.863
Anorexia	2 (3%)	0 (0%)	2 (8%)	0.190
Diarrhea	15 (25%)	9 (27%)	6 (23%)	0.713
Headache	2 (3%)	0 (0%)	2 (8%)	0.190

Data are median (IQR), n (%), or n/N (%), where N is the total number of patients with available data. p values comparing severe with non-severe patients were calculated by $\chi 2$ test, Fisher's exact test, or Mann-Whitney U test, as appropriate. COVID-19, coronavirus disease 2019.

The most common symptoms were fever (83%), cough (73%), fatigue (47%) and dyspnea (42%). Dyspnea was more common in severe patients compared to non-severe patients (65% vs. 24%, $p = 0.001$) (Table 1).

Laboratory findings of non-severe and severe COVID-19 patients with chronic airway diseases

When compared with non-severe patients, severe patients were more likely to have elevated neutrophil counts (8.2 vs. 4.1 × 10⁹/L, $p = 0.001$), decreased lymphocyte counts (0.6 vs. 1.1 × 10⁹/L, $p < 0.001$), eosinopenia (< 0.02 × 10⁹/L, 73% vs. 24%, $p < 0.001$), elevated d-dimer (> 1 μg/mL, 88% vs. 42%, $p = 0.001$), increased lactate dehydrogenase (LDH) (471.0 vs. 230.0 U/L, $p < 0.001$), elevated blood urea nitrogen (> 9.5 mmol/L, 42% vs. 3%, $p < 0.001$), increased hypersensitive troponin I (> 34 pg/mL, 48% vs. 7%, $p = 0.001$), and increased inflammation markers including C-reactive protein (CRP) (126.2 vs. 19.9 mg/L, $p < 0.001$), procalcitonin (≥ 0.05 ng/mL, 96% vs. 43%, $p < 0.001$) and ferritin (1264.2 vs. 293.6 mg/L, $p = 0.004$) (Table 2). Of note, significant differences in the expression of inflammation-related cytokines including interleukin (IL)-6, IL-8 and tumor necrosis factor (TNF)-α were observed between the two groups, which were dramatically increased in severe patients.

Table 2
Laboratory findings of COVID-19 patients with chronic airway inflammation on admission.

	Normal range	All patients (n = 59)	Non-severe patients (n = 33)	Severe patients (n = 26)	p value
White blood cell count, × 10⁹/L	4.00–10.00	6.66 (4.54–9.61)	5.98 (3.71–7.43)	9.27 (5.86–12.83)	0.002
<4		13 (22%)	9 (27%)	4 (15%)	0.004
4–10		33 (56%)	22 (67%)	11 (42%)	
>10		13 (22%)	2 (6%)	11 (43%)	
Neutrophil count, × 10⁹/L	1.80–6.30	4.50 (2.73–7.99)	4.12 (2.36–5.42)	8.16 (3.90–12.00)	0.001
Lymphocyte count, × 10⁹/L	1.10–3.20	0.84 (0.53–1.44)	1.14 (0.80–1.73)	0.56 (0.28–0.76)	0.000
<1·1		38 (64%)	16 (48%)	22 (85%)	0.004
≥1·1		21 (36%)	17 (52%)	4 (15%)	
Macrophages, × 10⁹/L	0.10–0.60	0.51 (0.35–0.63)	0.51 (0.36–0.66)	0.52 (0.33–0.63)	0.891
Eosinophil count, × 10⁹/L	0.02–0.52	0.02 (0.00-0.08)	0.04 (0.02–0.11)	0.00 (0.00-0.02)	0.000
<0.02		27 (46%)	8 (24%)	19 (73%)	0.000
≥0.02		32 (54%)	25 (76%)	7 (27%)	
Basophils, × 10⁹/L	0.00-0.10	0.01 (0.01–0.03)	0.01 (0.01–0.03)	0.01 (0.01–0.03)	0.657
Haemoglobin, g/L	130.0-175.0	129.0 (112.0-139.0)	134.0 (116.5–141.0)	125.5 (109.0-134.8)	0.184
Platelet count, × 10⁹/L	125.0-350.0	213.0 (143.0-272.0)	216.0 (166.0-279.5)	176.0 (85.5-244.5)	0.145
<125		10 (17%)	2 (6%)	8 (31%)	0.012
≥125		49 (83%)	31 (94%)	18 (69%)	
Ferritin, μg/L	30–400	534.60 (219.80-1355.63)	293.55 (201.90–581.00)	1264.20 (577.45-1889.55)	0.004

Data are median (IQR), n (%), or n/N (%), where N is the total number of patients with available data. p values comparing severe with non-severe patients were calculated by $\chi 2$ test, Fisher's exact test, or Mann-Whitney U test, as appropriated. COVID-19, coronavirus disease 2019

infection.

	Normal range	All patients (n = 59)	Non-severe patients (n = 33)	Severe patients (n = 26)	p value
Erythrocyte sedimentation rate, mm/H	0–15	31.50 (15.00-59.75)	40.00 (16.50–59.50)	26.00 (15.00–74.00)	0.872
D-dimer, μg/mL	≤ 0·5	1.73 (0.49–2.74)	0.65 (0.40–2.17)	2.69 (1.44–8.99)	0.001
≤0·5		14/57 (25%)	12/31 (39%)	2 (8%)	0.001
>0·5 to ≤ 1		7/57 (12%)	6/31 (19%)	1 (4%)	
>1		36/57 (63%)	13/31 (42%)	23 (88%)	
Creatine kinase, U/L	≤ 190	85.50 (47.50–196.00)	65.00 (38.00-162.25)	127.00 (60.50-446.50)	0.065
Lactate dehydrogenase, U/L	135–225	260.00 (223.00-471.00)	230.00 (200.00-280.00)	471.00 (291.00-628.00)	0.000
≤225		15 (25%)	14 (42%)	1 (4%)	0.001
>225		44 (75%)	19 (58%)	25 (96%)	
Hypersensitive troponin I, pg/mL	≤ 34.2	7.60 (3.03–44.70)	4.10 (1.95–14.15)	33.40 (4.55-281.85)	0.001
≤34.2		40/54 (74%)	27/29 (93%)	13/25 (52%)	0.001
>34.2		14/54 (26%)	2/29 (7%)	12/25 (48%)	
Alanine aminotransferase, U/L	≤ 41	24.00 (15.00–40.00)	22.00 (14.00-39.50)	24.50 (17.50–69.00)	0.205
≤41		45 (76%)	27 (82%)	18 (69%)	0.259
>41		14 (24%)	6 (18%)	8 (31%)	
Aspartate aminotransferase, U/L	≤ 40	32.00 (19.00–50.00)	23.00 (18.50–39.50)	45.50 (21.50-89.25)	0.003
≤40		37 (63%)	26 (79%)	11 (42%)	0.004
>40		22 (37%)	7 (21%)	15 (58%)	

Data are median (IQR), n (%), or n/N (%), where N is the total number of patients with available data. p values comparing severe with non-severe patients were calculated by $\chi 2$ test, Fisher's exact test, or Mann-Whitney U test, as appropriated. COVID-19, coronavirus disease 2019

infection.

	Normal range	All patients (n = 59)	Non-severe patients (n = 33)	Severe patients (n = 26)	p value
Blood urea nitrogen, mmol/L	3.6–9.5	5.10 (3.80–8.30)	4.70 (3.75–5.60)	7.90 (4.50-15.15)	0.004
≤9.5		47 (80%)	32 (97%)	15 (58%)	0.000
>9.5		12 (20%)	1 (3%)	11 (42%)	
Creatinine, μmol/L	59–104	74.00 (61.00–94.00)	72.00 (61.00-86.50)	80.50 (60.00-123.25)	0.136
≤104		49 (83%)	32 (97%)	17 (65%)	0.001
>104		10 (17%)	1 (3%)	9 (35%)	
Procalcitonin, ng/mL	< 0.05	0.08 (0.04–0.31)	0.04 (0.03–0.07)	0.18 (0.08–1.37)	0.000
<0·05		18/55 (33%)	17/30 (57%)	1/25 (4%)	0.000
≥0·05		37/55 (67%)	13/30 (43%)	24/25 (96%)	
High-sensitivity C-reactive Protein (hs-CRP), mg/L	< 1	30.55 (4.33-124.28)	19.85 (1.93–34.05)	126.15 (27.68-188.43)	0.000
<3		14/58 (24%)	11/32 (34%)	3 (12%)	0.043
≥3		44/58 (76%)	21/32 (66%)	23 (88%)	
IL-1β, pg/mL	< 5	5.00 (5.00–5.00)	5.00 (5.00–5.00)	5.00 (5.00–5.00)	0.245
IL-2R, U/L	223–710	645.00 (406.50–1068.00)	499.50 (337.25-734.25)	973.00 (602.00-1919.00)	0.000
IL-6, pg/mL	< 7	11.59 (2.34-57.00)	5.68 (1.83–29.56)	47.42 (8.64–167.20)	0.002
IL-8, pg/mL	< 62	14.40 (7.90–47.10)	11.20 (5.40-21.05)	34.10 (12.95-81.00)	0.001
IL-10, pg/mL	< 9.1	5.00 (5.00-7.20)	5.00 (5.00–5.00)	6.30 (5.00-19.45)	0.001
TNFα, pg/mL	< 8.1	9.20 (5.75–12.90)	7.65 (4.60-10.83)	11.80 (7.50–17.30)	0.021

Data are median (IQR), n (%), or n/N (%), where N is the total number of patients with available data. p values comparing severe with non-severe patients were calculated by $\chi 2$ test, Fisher's exact test, or Mann-Whitney U test, as appropriated. COVID-19, coronavirus disease 2019

infection.

Predictors of the severity of COVID-19 patients with chronic airway diseases

To identify the predictors of the severity of COVID-19 patients with chronic airway diseases, we analyzed the association between the abnormal laboratory findings and the disease severity with univariate and multivariate logistic regression models. The disease severity was significantly associated with all of the above mentioned abnormal laboratory findings in univariate logistic regression analyses. In a multivariate regression model incorporated lymphopenia, eosinopenia, elevated LDH and increased IL-6, eosinophil counts < 0.02 × 10⁹/L (odds ratio per 1 unit increase, 10.115 [95% CI 2.158–47.414], $p = 0.003$) and LDH levels > 225 U/L (odds ratio per 1 unit increase, 22.300 [2.179-228.247], $p = 0.009$) were independent risk factors for disease severity (Table 3). Our data suggest that decreased eosinophil counts and increased LDH levels may help the clinician to identify the severe COVID-19 patients with chronic airway diseases.

Table 3
Predictors of disease severity in COVID-19 patients with chronic airway diseases.

	Univariable OR (95% CI)	p value	Multivariable OR (95% CI)	p value
Laboratory findings				
White blood cell count, × 10⁹/L	1.296(1.087–1.546)	0.004	..	..
<4	0.889(0.223–3.542)	0.867	..	..
4–10	1 (ref)	..	..	..
>10	11.000(2.068–58.519)	0.005	..	..
Neutrophil count, × 10⁹/L	1.397(1.136–1.718)	0.002	..	..
Lymphocyte count, × 10⁹/L	0.204(0.068–0.615)	0.005	..	..
<1.1	5.844(1.649–20.712)	0.006	..	..
≥1.1	1 (ref)	..	..	..
Macrophages, × 10⁹/L	0.792(0.084–7.486)	0.839	..	..
Eosinophil count, × 10⁹/L*	5.031×10^{-8} (3.962×10^{-14}-0.064)	0.019	..	..
<0.02	8.482(2.615–27.515)	0.000	10.115(2.158–47.414)	0.003
≥0.02	1 (ref)	..	1 (ref)	..
Basophils, × 10⁹/L	0.003(4.819×10^{-16}-1.404×10^{10})	0.691	..	..
Platelet count, × 10⁹/L	0.996(0.990–1.001)	0.117	..	..
<125	6.889(1.317–36.042)	0.022	..	..
≥125	1 (ref)	..	..	..
Ferritin, μg/L	1.002(1.000-1.003)	0.011	..	..
Erythrocyte sedimentation rate, mm/H	1.001(0.980–1.023)	0.896	..	..
D-dimer, μg/mL	1.305(0.981–1.736)	0.067	..	..
≤0·5	1 (ref)	..	..	..
>0·5 to ≤ 1	1.000(0.075–13.367)	1.000	..	..

OR = odds ratio. *Per 1 unit increase.

	Univariable OR (95% CI)	p value	Multivariable OR (95% CI)	p value
>1	10.615(2.051–54.954)	0.005	..	..
Creatine kinase, U/L	1.005(0.999–1.010)	0.090	..	..
Lactate dehydrogenase, U/L*	1.014(1.006–1.022)	0.000	..	..
≤225	1 (ref)	..	1 (ref)	..
>225	18.421(2.223-152.647)	0.007	22.300(2.179-228.247)	0.009
Hypersensitive troponin I, pg/mL	1.012(0.998–1.027)	0.085	..	..
≤34.2	1 (ref)	..	..	..
>34.2	0.080(0.016–0.412)	0.003	..	..
Aspartate aminotransferase, U/L	1.040(1.012–1.069)	0.005	..	..
≤40	1 (ref)	..	..	..
>40	5.065(1.618–15.853)	0.005	..	..
Blood urea nitrogen, mmol/L	1.269(1.068–1.508)	0.007	..	..
≤9.5	1 (ref)	..	..	..
>9.5	23.467(2.769-198.859)	0.004	..	..
Creatinine, μmol/L	1.022(1.001–1.044)	0.041	..	..
≤104	1 (ref)	..	..	..
>104	16.941(1.977–145.160)	0.010	..	..
Procalcitonin, ng/mL	390.345(1.993-76464.041)	0.027	..	..
<0.05	1 (ref)	..	..	..
≥0.05	31.385(3.742-263.235)	0.001	..	..
High-sensitivity C-reactive Protein (hs-CRP), mg/L	1.023(1.010–1.036)	0.001	..	..
<3	1 (ref)	..	..	..
≥3	4.016(0.983–16.400)	0.053	..	..
IL-2R, U/ml	1.003(1.001–1.004)	0.005	..	..

OR = odds ratio. *Per 1 unit increase.

	Univariable OR (95% CI)	p value	Multivariable OR (95% CI)	p value
IL-6, pg/ml	1.023(1.003–1.044)	0.022	..	..
<7	1 (ref)	..	..	..
≥7	8.000(1.908–33.537)	0.004	..	..
IL-8, pg/mL	1.026(1.002–1.051)	0.030	..	..
IL-10, pg/mL	1.166(0.999–1.363)	0.052	..	..
TNF-α, pg/ml	1.178(1.024–1.355)	0.022	..	..
OR = odds ratio. *Per 1 unit increase.				

Eosinophil counts and LDH levels tend to return to normal range over time in non-severe patients

We further analyzed the eosinophil counts and LDH levels in non-severe and severe COVID-19 patients with chronic bronchitis, COPD, and asthma, respectively. We found that there was a significant difference in eosinophil counts and LDH levels between severe and non-severe patients with chronic bronchitis and COPD whereas not in patients with asthma (Fig. 1). To observe the dynamic changes of eosinophil counts and LDH levels over time, we collected the eosinophil counts and LDH levels on the 5th, 10th, 15th, 20th, 25th, and 30th day after admission. We found that eosinophil counts increased over time both in severe and non-severe patients. Meanwhile, LDH decreased over time (Fig. 2). Severe patients showed a slower recovery rate than non-severe patients, especially eosinophil counts. Of note, both eosinophil counts and LDH levels recovered more slowly in severe patients with COPD than those in severe patients with chronic bronchitis and asthma. Our data suggest that, as the disease improved, eosinophil counts and LDH levels tend to return to normal range both in severe and non-severe patients, indicating a good therapeutic effect of patients with chronic airway diseases in COVID-19 treatment.

We further performed multivariate analysis for mortality in COVID-19 patients with chronic airway inflammation using the above four variables and found that eosinophil counts < 0.02 × 10⁹/L (odds ratio per 1 unit increase, 18.000 [95% CI 1.929-167.986], $p = 0.011$) was the only independent risk factor for mortality (Supplementary Table 1). Moreover, Kaplan-Meier survival curves indicated that COVID-19 patients with eosinopenia or elevated LDH had worse survival probability ($p < 0.05$) (Supplementary Fig. 1). This suggests that eosinopenia and elevated LDH are also potential predictors for the mortality of COVID-19 patients with underlying chronic airway diseases.

Discussion

In this retrospective cohort study, we found that eosinophil counts less than 0.02 × 10⁹/L and LDH levels greater than 225 U/L on admission were associated with the severity of COVID patients with underlying chronic bronchitis, COPD and asthma. Moreover, eosinophil counts and LDH levels tend to return to a normal range in severe and non-severe patients after treatment.

Circulating and tissue-resident eosinophils are associated with a variety of diseases, in which eosinophils participate in the pathological process and play a potent proinflammatory role, such as COPD, asthma, and chronic bronchitis. Previously, human eosinophil has been reported to play an important role in virus detection and defending through several Toll-like receptors (TLRs), including TLR1, TLR3, TLR4, TLR7, TLR9, and TLR10 [18–21]. Single-stranded RNA viruses, such as coronavirus, can be recognized by eosinophils in the airway tract through TLR7, whose subsequent stimulation triggers eosinophil cytokine expression and nitric oxide (NO) generation to promote viral clearance [19–22]. In view of elevated eosinophils in patients with chronic airway inflammation, COPD, asthma and chronic bronchitis have not yet been reported as major risk factors for the severity of SARS-CoV-2 infections. According to an ambispective cohort study of 548 COVID-19 patients, only 5 cases of asthma were identified, significantly lower than previously reported asthma prevalence in Wuhan (6.4%) [23–26]. Zhang et al recently reported that none had asthma or other comorbid atopic diseases and only two patients had COPD (1.4%) in a cohort of 140 hospitalized COVID-19 patients, more than half of whom (53%) had eosinopenia on the day of hospital admission [23]. Similarly, Du et al analyzed clinical features of 85 fatal cases of COVID-19 and found that 81% of the patients had very low eosinophil counts on admission [27]. In our cohort including 1 888 patients, 31 patients had chronic bronchitis (1.64%), 18 patients had COPD (0.95%) and only 10 patients had asthma (0.53%). Circulating eosinophil counts were reported to gradually increase over the time in COVID-19 and were synchronous with the improvement of chest CT, revealing the effective role of eosinophil in the prognosis monitoring of COVID-19 patients [14]. Liu et al also suggested that elevated eosinophils might be an indicator for COVID-19 improvement in a small cohort of COVID-19 patients [28]. A recent study has highlighted the significant role of $CD101^{-}$ eosinophils in suppressing acute lung injury and respiratory failure [29]. Therefore, eosinophil could have helped patients with chronic airway inflammation escape from SARS-CoV-2 infections and has been identified as a probable potential indicator for prognosis in COVID-19. Jackson et al found a negative correlation between ACE2 expression in airway epithelium and peripheral blood eosinophil counts, which could explain the reason why severe patients were more vulnerable to SARS-CoV-2 infection [30]. Meanwhile, eosinopenia was more common in critically severe patients, suggesting that the resolution of eosinopenia could be a possible way to improve clinical status [31].

In our study, lower expression of eosinophil showed worse survival probability and eosinophil counts significantly decreased in severe COVID-19 patients with chronic bronchitis and COPD. No significant difference was observed in asthma patients, partly due to the limited sample size. We further explored dynamic changes of eosinophil counts in patients with chronic airway diseases in the course of COVID-19 and found that eosinophil counts gradually increased over time and returned to normal range in both severe and non-severe patients. It still remains unclear how eosinopenia takes place in COVID-19, but possible mechanisms of decreasing eosinophils could be inhibition of eosinopoiesis and egress of eosinophils from the bone marrow [32, 33], the reduction of chemokine receptors or adhesion factors [34], and interferon (IFN) mediated eosinophil apoptosis during the virus infection [33].

LDH has long been reported to be associated with COPD, asthma, and chronic bronchitis and identified as a potential marker of chronic airway inflammation [35–37]. Meanwhile, a large number of studies reported elevated LDH levels in COVID-19, which could be a risk factor of mortality [10–12, 38–41]. Zheng et al conducted a systematic literature review and meta-analysis including 4 studies, a total of 1286 cases, and found that LDH was statistically significantly higher in severe patients compared to non-severe patients [38]. Elevated LDH in severe cases indicated diffuse lung injury and tissue damage [38, 42], therefore, we hypothesized that LDH might be another predictor of chronic airway inflammation exacerbation in COVID-19. Kaplan-Meier survival analysis suggested the hazard of elevated LDH levels. Similar to eosinophil, LDH showed elevated levels in severe COVID-19 patients with chronic bronchitis and COPD, and gradually decreased over time in severe and non-severe COVID-19 patients.

Previous studies have identified older age as a risk factor of mortality in SARS, MERS, and COVID-19 [10–12, 43–45]. However, in our study, age had no statistic difference between severe and non-severe patients, partly due to epidemiological characteristic in respiratory diseases with chronic airway inflammation, since such patients were commonly old regardless of disease severity. Lymphocytopenia was also associated with poor outcomes in our cohort (85%), which is consistent with other reports [40, 46]. Impaired lymphogenesis or increased apoptosis could explain lymphocytopenia in severe cases of COVID-19 [47]. Of note, d-dimer levels greater than 1 μg/L were more common in severe patients compared to non-severe patients, which was reported as a risk factor for mortality of adult inpatients with COVID-19 [10].

Accumulating evidence reveals that cytokine storm plays a crucial role in the pathogenesis of COVID-19. Extremely increased inflammatory parameters, including CRP and proinflammatory cytokines (IL-6, TNFα, IL-8, et al) were recently reported in critical COVID-19 patients [48]. Th1-dominated responses with significantly elevated cytokines (INF-γ, IL-1β, IL-6, IL-8, IL-12, and TNF-α) were shown previously in plasma cytokine profiles of SARS patients, giving rise to the recruitment of alveolar macrophages and the development of ARDS [49–51]. Similarly, a predominant Th1 and Th17 cytokine profile with elevated IFN-γ, TNF-α, IL-10, IL-15, and IL-17 was reported during the acute phase of MERS-CoV infection [52]. In our cohort, severe patients had markedly higher levels of CRP, procalcitonin, IL-2R, IL-6, IL-8, and TNF-α. Notably, several reports confirmed the elevation of serum IL-6 in critically ill patients with COVID-19, suggesting that mortality might be associated with virally driven hyperinflammation and IL-6 played a predominant role in cytokine release syndrome [10, 11, 41, 48, 53–55]. Tocilizumab (IL-6 receptor blockade) has been approved in some patients with COVID-19 pneumonia, offering an effective treatment option for severe patients [53, 56].

Our study had some limitations. Firstly, due to the retrospective study design, the accuracy of all laboratory results was dependent upon medical records. Observation bias might also exist in this study due to the limited sample size. Secondly, there could be a selection bias in the multivariate regression model when analyzing the risk factors.

Conclusion

Our study reveals that eosinopenia and elevated LDH on admission are potential predictors of disease severity in adults with COVID-19 and underlying chronic airway diseases. These predictors may help clinicians identify the severe COVID-19 patients with chronic bronchitis, COPD, and asthma.

Methods

1. Study population and data collection

Subjects of this study were adults with COVID-19 and underlying chronic respiratory diseases (admission date from Jan 26th to April 3rd, 2020) in Sino-French New City Branch of Tongji hospital. COVID-19 patients were diagnosed according to World Health Organization (WHO) interim guideline [57]. All patients were confirmed by the positive findings in reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay of SARS-CoV-2 RNA in throat swab specimens. The study was approved by the Institutional Review Board of Tongji Hospital, Huazhong University of Science and Technology.

The demographic information, clinical characteristics (included medical history, symptoms, comorbidities, smoking history, and allergic history) and radiological results of each patient were obtained from the electronic medical record system of Sino-French New City Branch of Tongji hospital and analyzed by three independent researchers. The severity of COVID-19 was staged according to the guidelines for diagnosis and treatment of COVID-19 published by Chinese National Health Committee (Version 5-7).

2. The criteria for the severity of COVID-19

Severe COVID-19 patients were diagnosed when conforming to one of the following criteria: 1) Respiratory distress with respiratory frequency ≥ 30/min; 2) Pulse Oximeter Oxygen Saturation ≤ 93% at rest; 3) Oxygenation index (artery partial pressure of oxygen/inspired oxygen fraction, PaO2/FiO2) ≤ 300 mmHg.

3. Laboratory testing

Medical laboratory finding results, including the numbers of leucocytes, lymphocytes, monocytes, eosinophils, basophils, platelets, Alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum creatine kinase (CK), serum lactic dehydrogenase (LDH), blood urea nitrogen (BUN), serum creatinine (Scr), cardiac troponin I, concentrations of D-dimer, C-reactive protein (CRP), procalcitonin (PCT), erythrocyte sedimentation rate (ESR), serum ferritin, cytokines (IL-2R, IL-6, IL-8, IL-10, TNF-α), immune function were collected for each patient from electronic medical records.

4. Statistical analysis

All data were analyzed with SPSS Statistics Software (version 26; IBM, New York, USA). The statistics for categorical variables were summarized as frequencies and percentages and were compared using Chi-square test or Fisher's exact test between different groups where appropriate. Continuous variables were

described using median (IQR) and compared using Mann-Whitney U test. To explore the risk factors associated with disease severity, univariable and multivariable logistic regression models were used to estimate odds ratios and the 95% confidence intervals. A two-sided α of less than 0.05 was considered statistically significant.

Declarations

Authors' contributions

LY and GZ conceptualized the study design. LY, DC, SZ, YF, WW, CC, SC collected demographic, clinical, and laboratory data. LY, DC, SZ, YF and GZ analyzed the data. LY and DC interpreted the results. LY, DC and GZ wrote the manuscript with all authors providing feedback for revision. All authors read and approved the final report.

Acknowledgments

We are sincerely thankful to all front-line members of the medical, nursing, and support staffs of the Sino-French New City Branch of Tongji Hospital for their support and sacrifice.

Funding

Supported by National Natural Science Foundation of China (grants 81800026, 81670019, 91742108), National Key Research and Development Program of China (2016YFC1304400).

Ethics approval and consent to participate

This retrospective study was approved by the institutional ethics board of Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology. Written informed consent was waived.

Consent for publication

Not applicable.

Competing interests

The authors have no competing interests to declare.

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Figures

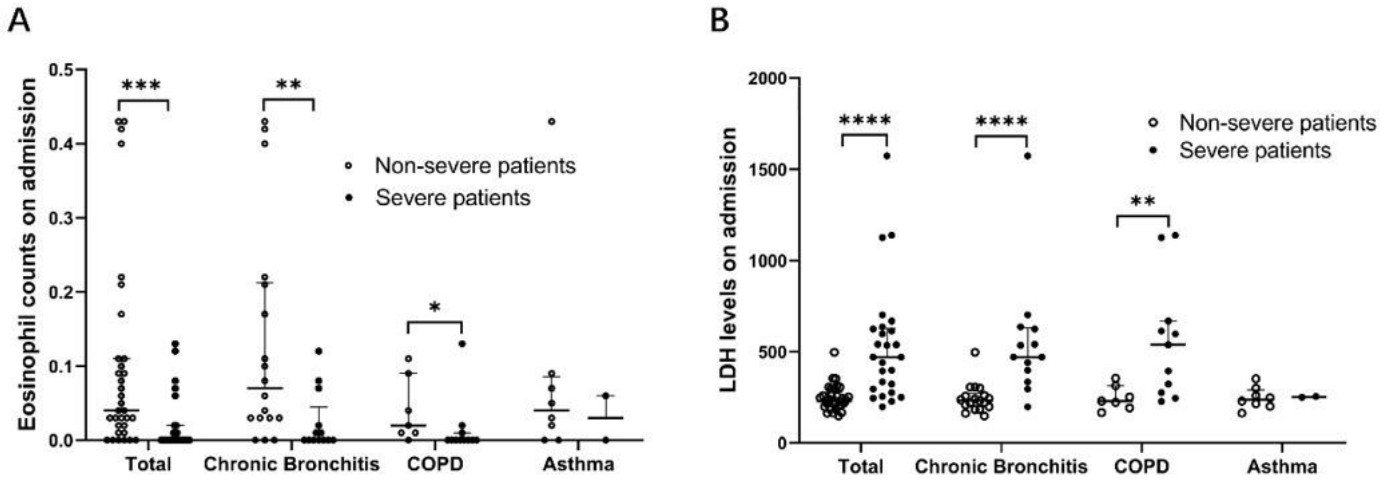

Figure 1

Clinical characteristics of eosinophil and LDH in COVID-19 patients with chronic airway inflammation. (A) Eosinophil counts in different subgroups. Eosinophil counts were significantly decreased in severe COVID-19 patients with chronic bronchitis and COPD; (B) LDH levels in different subgroups. LDH levels were significantly decreased in severe COVID-19 patients with chronic bronchitis and COPD. Values of non-severe and severe patients were presented with open and closed circles, respectively. Mann-Whitney U test was used. *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001.

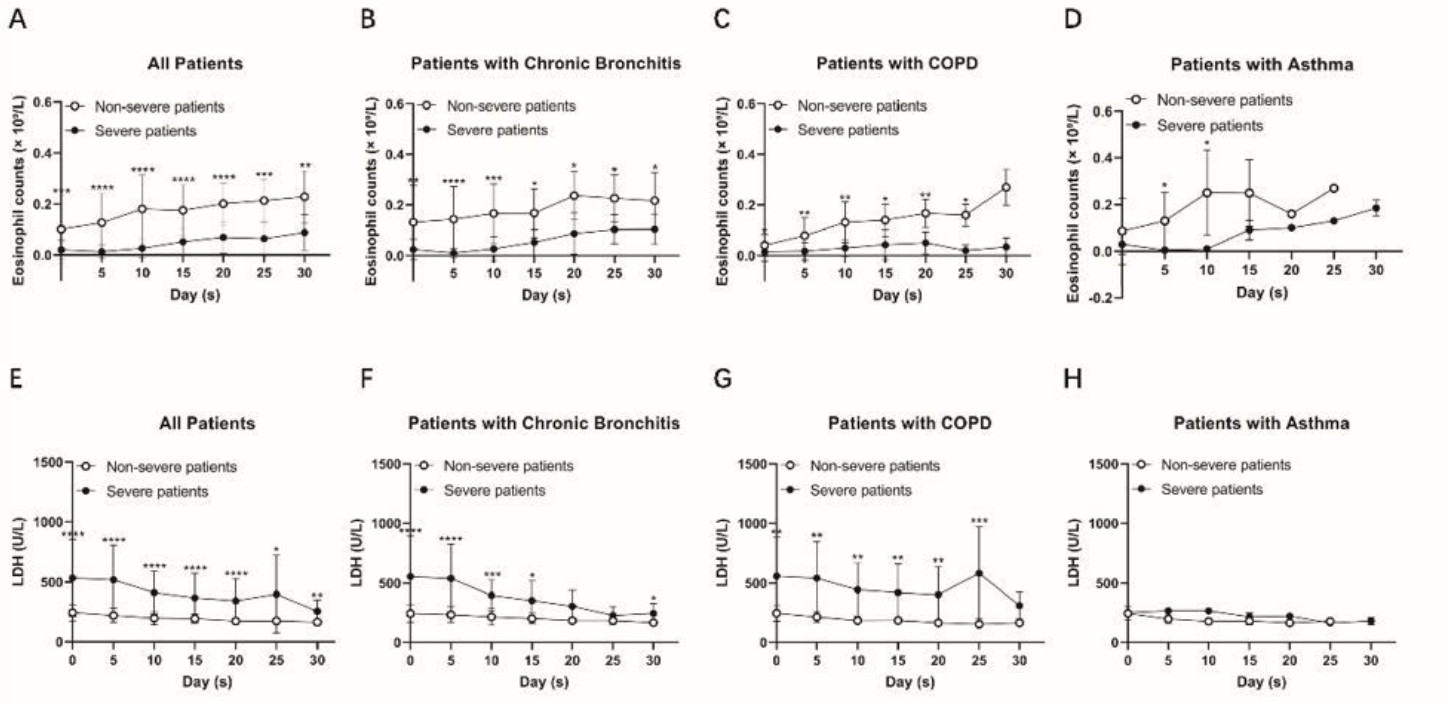

Figure 2

Dynamic changes of eosinophil counts and LDH levels in COVID-19 patients with chronic airway diseases. (A-D) Eosinophil counts increased over time in non-severe and severe COVID-19 patients with chronic bronchitis (n = 31), COPD (n = 18) and asthma (n = 10). (E-H) LDH levels decreased over time in non-severe and severe COVID-19 patients with chronic bronchitis (n = 31), COPD (n = 18) and asthma (n = 10). Values of non-severe and severe patients were presented with open and closed circles, respectively. Mann-Whitney U test was used. *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001, compared with the eosinophil counts or LDH levels between severe and non-severe patients.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplymentarydata.pdf