Protective Factors and Risk Factors in Patients with COVID-19 Pneumonia and/or Infection

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Research article

Keywords: COVID-19, lung CT-negative, protective factors, risk factors, repeatedly negative and positive nucleic acid tests

Posted Date: June 25th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-36747/v1

Abstract

This study examined 50 COVID-19 patients who have been cured in Anhui Province, China. The protective factors and risk factors for these patients were investigated. By comparing CT-negative and CT-positive patients, we found protective factors in blood: lymphocytes, eosinophils number and %, basophils%, reticulocyte%, high fluorescence reticulocyte ratio, and reticulocyte absolute value. Comparing patients with underlying disease and without underlying disease, we found protective factors in blood: lymphocytes%, basophils%, large platelets, and low-fluorescent reticulocyte ratio. Regarding the biochemistry indicators, albumin/globulin, apolipoprotein and prealbumin can be considered as protective factors for patients without lung symptoms. Urea, glucose, total bile aicd, creatinine and hypersensitivity CRP can be considered as risk factors for patients with underlying diseases. For patients with repeatedly negative and positive results in nucleic acid tests, they were at a medium level in terms of both protective and risk factors, explaining the mild symptoms and repeatedly results in nucleic acid tests.

Background:

Since the outbreak of the COVID-19 pneumonia in Wuhan in December 2019, the epidemic situation has progressed rapidly (Varadi et al. 2020). By April 2020, the epidemic has progressed to the most countries and regions in the world (Ivorra et al. 2020). Studies have shown that the source of infection is mainly COVID-19 infected patients and asymptomatic carriers (Phan et al. 2020). Respiratory droplets and contact transmission are main routes of transmission, and aerosol and fecal-oral transmission have also been identified as routes of transmission (Lu et al. 2020). The epidemic situation in China is currently under control (Lancet, 2020), but the emergence of patients who tested positive after treatment and discharged from hospital brought huge challenges to the prevention and control of the epidemic (Lan et al. 2020).

Compared with the original reverse transcription polymerase chain reaction (RT-PCR), chest CT is more sensitive to the diagnosis of COVID-19 (Li et al. 2020). The positive rate of RT-PCR and chest CT examination in the cohort was 59% (601/1014) and 88% (888/1014) (Tenda et al. 2020), respectively. With RT-PCR as reference, the sensitivity of chest CT examination increased to 97% (580/601) (Zhang et al. 2020). Among patients with negative RT-PCR results but positive chest CT scans (308), 48% (147/308) were reconsidered as highly probable cases (Huang et al. 2020). The CT positive manifestations in lungs were indicators of pneumonia (Meng et al. 2020), and the results in CT scan can be used to distinguish COVID-19 pneumonia from infection without pneumonia. In our sample, at least half of the patients did not have lung symptoms but infected with the COVID-19 virus.

In order to further improve the prevention and control of the COVID-19 epidemic, this study investigated a group case of the hospital in Hefei, China, aiming to figure out the biochemical and blood routine differences between COVID-19 pneumonia and infection (without pneumonia) patients. The study figured out the protective factors and risk factors from biochemical examination and blood routine examination, and also investigated three patients with repeatedly negative and positive results in nucleic acid tests. Here, we reported the epidemiological, clinical, radiological and laboratory findings of 50 patients (pneumonia and infection).

Methods:

1. Cases

We enrolled 50 patients (26 pneumonia patients) who initially presented to the Second People's Hospital of Hefei and the First Affiliated Hospital of Anhui Medical University with fever, and/or respiratory symptoms, and/or pulmonary infiltrates on chest radiographs. The patients with confirmed diagnosis were implemented and reported according to ‘Technical Guidelines for Laboratory Testing of Pneumonia of New Coronary Disease Infection (Seventh Edition)’ of the National Health and Health Commission (National Health Commission of China).

All patients had mild to moderate symptoms without signs of life dying. We recorded and analyzed the history, physical findings, haematological, biochemical, radiological, and microbiological investigation results. Briefly, nasopharyngeal and throat swabs and stool samples were taken and put into viral transport media. This study was approved by the Institutional Review Board of the University of Anhui Medical University. We obtained written consent from the patients.

2. In-house one-step real-time RT-PCR assay

Pharyngeal swab nucleic acid test was assessed by Yaohai District Center for Disease Control and Prevention in Hefei, using fluorescent PCR method. A QIAamp Viral RNA Mini Kit (Qiagen, Hilden, Germany) was used to extract samples from each patient into 50 μL of eluate. Forward (5′-CCTACTAAATTAAATGATCTCTGCTTTACT-3′) and reverse (5′-CAAGCTATAACGCAGCCTGTA-3′) primers target the S gene of COVID-19 for determination. Real-time RT-PCR analysis was performed using the QuantiNova SYBR Green RT-PCR Kit (Qiagen) in a LightCycler 480 Real-Time PCR System (Roche, Basel, Switzerland). Reactions were incubated at 50 °C for 10 min and 95 °C for 2 min, followed by 45 cycles at 95 °C for 5 s and 60 °C for 30 s, and then subjected to melting curve analysis (95 °C for 5 s, 65 °C for 1 min, followed by a gradual increase in temperature to 97 °C with continuous recording of fluorescence).

3. Respiratory pathogen detection

Respiratory samples of the patients were tested for influenza A and B viruses and respiratory syncytial virus using the Xpert Xpress Flu/RSV assay (GeneXpert System, Cepheid, Sunnyvale, CA, USA). Samples were then tested using BioFire FilmArray Respiratory Panel 2 plus (bioMérieux, Marcy l’Etoile, France), to

detect the presence of respiratory microbial pathogens (including Coronaviruses, Legionella pneumophila, Mycoplasma pneumoniae, Rickettsia Q, Chlamydia pneumoniae, Adenovirus, Respiratory syncytial virus, Influenza A virus, Influenza B virus, Parainfluenza virus).

4. Lab Tests

The three major routines were blood routine, urine routine, and feces routine. The mainly checked items in blood tests included: red blood cells, hemoglobin, white blood cells, platelet counts, absolute lymphocyte values, absolute intermediate cells, absolute neutrophils, lymphocyte percentage, intermediate cell percentage, neutral percentage of granulocytes, hematocrit, average red blood cell volume, average red blood cell hemoglobin, average hemoglobin concentration, red blood cell distribution width, average platelet volume, platelet distribution width, platelet hematology, etc. Secondly, the main items of urine routine were: urine color, urine pH value, urine specific gravity, and protein qualitative and microscopic examination. Thirdly, the main items of feces routine were: stool color, hardness and mucus. Microscopic examination of the stool for helminthiasis (hookworm eggs, roundworm eggs, whipworm eggs) and other parasites.

5. CT of Lungs

Using Siemens somatom definition 64-row spiral CT scan, patient took the supine position, with the head in advance, patient was told to hold the breath during the scan. The scanning range was from the top to the bottom of two lungs and cross-sectional. the scanning parameters were: tube voltage 120 kV, tube current 320 mA, matrix 512*512, layer thickness and layer moment 5 mm.

Generally, in patients with COVID-19 pneumonia, the texture of two lungs was typically enhanced, blurred, and disordered. Multiple patchy ground-glass density lesions and consolidation lesions were seen on both lungs, with the bronchial vascular bundles and subpleural distribution predominantly. The shadow of blood vessels was thickened, and the shadow of bronchial was partially visible. The bronchial opening of each leaf was usually not obstructed. No obvious enlarged lymph nodes were seen in the mediastinum. The rib cages were symmetrical, there was no effusion in the chest cavity.

6. Treatment

All patients were actively treated after admission, with daily droplet isolation, air isolation, contact isolation, routine care for Class A infectious diseases, lopinavir/ritonavir tablets 500 mg x 2 per day, 2 ml saline nebulized inhalation, recombinant human interferon alpha 2b injection 5 million unit nebulized inhalation, Chinese medicine decoction, vitamin C tablet 0.2 g, abidol tablet 0.2 g, thymosin enteric-coated tablet 15 mg, chloroquine hydrogen sulfate tablet 300 mg. Patients all improved after 4–34 days treatment and were discharged from hospital. Three of them were re-examined after discharged and were hospitalized again because of positive results in the follow-up nucleic acid tests.

7. Statistics

We divided all patients into two groups, lung CT-positive and lung CT-negative. After age and gender matching, we performed independent sample t-tests on blood routine indicators and biochemical indicators. Since patients were measured with blood routine and biochemical exams several times during the hospital stay, we choose the exam results measured when the symptoms were the most serious.

Some of patients had underlying diseases, and the patients with underlying diseases were more prone to infect COVID-19 (Huang et al. 2020; Barraquer et al. 1988) we divided the patients into two groups according to whether they have underlying diseases. After age and gender matching, we performed independent sample t-tests on blood routine indicators and biochemical indicators.

After above comparisons, we identified some indicators that were more prominent than others, we performed z-transformation on these indicators first and then added them into two indexes: I and J. Since there were three patients in our sample, who showed repeatedly negative and positive results in the nucleic acid tests, we extracted these three patients and placed them in the whole distribution of the sample for observation.

Results:

1. Lung CT-negative vs. Lung CT-positive:

We have 26 patients who were diagnosed with COVID-19 pneumonia, and 24 patients were diagnosed with COVID-19 infection without respiratory symptoms. Age range 12–87 years, with mean 48.20 and SD 16.06, 27 males. After gender and age matching, we had 22 in CT-positive group and 24 in CT-negative group.

By comparing two groups, we found that patients with CT-negative have the number of lymphocytes, number of eosinophils, percentage of eosinophils, number of basophils, the absolute value of reticulocytes, the percentage of reticulocytes and the ratio of high fluorescent reticulocytes greater than those of patients with CT-positive. $ps < 0.05$.

In addition, lung CT-negative patients had higher calcium, lower creatinine, higher urea creatinine ratio, lower globulin, higher albumin/globulin, lower creatinine, lower lactate dehydrogenase, higher HDL/CHOL, higher prealbumin, higher apolipoprotein a1 and lower SAA in blood than lung CT-positive patients. For results, see Table 1a,b and Fig. 1a,b.

2. Without-underlying diseases vs. with-underlying diseases

Twenty-three patients had underlying diseases before they were infected with COVID-19, the underlying diseases included hypertension (n = 10), hyperlipidemia (10), diabetes (5), rheumatoid arthritis(1), chronic bronchitis with emphysema (2), cervical spondylosis (1), femoral head necrosis (1), cerebral infarction (1), chronic hypothyroidism (1), fatty liver (1), chronic superficial gastritis (2), pregnancy (1), and lactation (1). After gender and age matching, we had 23 in with-underlying disease group and 24 in without-underlying disease group.

In patients without underlying diseases, lower number of neutrophils, lower number of monocytes, higher percentage of lymphocytes, higher percentage of basophils, greater number of large platelets, lower immature reticulocyte ratio, higher low-fluorescent reticulocyte ratio and lower medium-fluorescent reticulocyte ratio were found.

In addition, higher chloride, lower urea, lower creatinine, lower glucose, lower total bile acid, lower cystatin C, lower apolipoprotein B, lower hypersensitive CRP in blood were found in patients without underlying disease. For results, see Table 2a,b and Fig. 2a,b.

3. Three patients with repeatedly positive and negative nucleic acid tests

There were three patients with repeatedly positive and negative results in nucleic acid tests. Patient A, male, age 79, lung CT negative, with a history of chronic bronchitis with emphysema, cervical spondylosis, femoral head necrosis and cerebral infarction. In addition, he was in a family cluster case, with three of his family members diagnosed with COVID-19 pneumonia and four of his family members diagnosed with COVID-19 infection, including Patient B. He was staying in hospital for total 59 days, he has been tested with nucleic acid tests, including pharyngeal swabs and anal swabs, for 19 times, with 6 negative and 13 positive.

Patient B, female, age 34, lung CT negative, without an underlying disease. She was in the family cluster case with Patient A (her father-in-law). She was in hospital for total 63 days, and was tested with nucleic acid tests, including pharyngeal swabs and anal swabs, for 9 times, with 6 negative and 3 positive.

Patient C, male, age 44, lung CT positive, without an underlying disease. He was in hospital for total 35 days. He was tested with nucleic acid tests, including pharyngeal swabs and anal swabs, for 17 times, with 7 negative and 10 positive.

For the indicators most prominent in the tests 1 and 2 above, we performed z-transformation and added them into two indexes: I and J. Index I included albumin/globulin, apolipoprotein, and prealbumin. Index J included urea, glucose, total bile aicd, creatinine, and hypersensitivity CRP. We draw the distributions for I and J separately, and placed these three patients into the distributions for observation, as shown in Fig. 3a, b.

Discussion:

Most patients with COVID-19 pneumonia had typical imaging features, including ground glass opacity (GGO) (86%) or mixed GGO and merge (65%), dilated blood vessels at the lesion (72%) and traction bronchiectasis (53%). Disease changes usually have a surrounding distribution (88%), bilateral involvement (83%), and predominantly in the lower lobes (55%) and multi-focus (55%) (Zhao et al., 2020; Yang et al., 2020). CT in the middle-stage of the disease showed an increase in the number and size of GGO. CT found the highest severity visible around 10 days after the onset of symptoms. Acute respiratory distress syndrome was the most common indication for transferring COVID-19 patients to the ICU and was the major cause of death in these patients (Li et al. 2020). CT model corresponding to clinical improvement usually occurred after the second week of the disease, including the gradual resolution of comorbidities, the reduced number of turbidity, lesions and affected leaves (Salehi et al., 2020; Pan et al., 2020).

Consistent with the literature, our patients had the same features in lung CT scans. As our patients had mild to moderate symptoms, there were no case of death or ICU cases. The literature generally described CT findings in patients with COVID-19 pneumonia, and these CT features changed with the disease development, from mild to severe to death, and there were also CT features in the recovery period (Wang et al. 2020). However, no study has investigated the differences between patients with positive CT scans and negative CT scans in lungs.

We found that patients with CT-negative findings (infected patients) had the number of lymphocytes, number of eosinophils, percentage of eosinophils, number of basophils, the absolute value of reticulocytes, the percentage of reticulocytes, and the ratio of high fluorescent reticulocytes increased, compared to patients with CT-positive findings (pneumonia patients). Generally, elevated number of lymphocytes means a healthy immunity and resistance to viruses (Guan et al. 2020; Jiang et al. 2020). Therefore, the infected patients without pneumonia might have better immunity and hematopoietic function than patients with pneumonia. The chance for them to be infected in lungs became smaller and they were less threatened by death due to ARDS.

In addition, the infected patients had higher calcium, lower creatinine, higher urea creatinine ratio, lower globulin, higher albumin/globulin ratio, lower creatine creatinine, lower lactate dehydrogenase, higher HDL/CHOL, higher prealbumin, higher apolipoprotein a1, and lower SAA in blood than the pneumonia patients. In the infected but not pneumonia patients, calcium, urea/creatinine ratio, albumin/globulin ratio, HDL/CHOL ratio, prealbumin and apolipoprotein a1 became greater, indicating that these indicators may play a potentially protective role in fighting COVID-19 viruses.

In patients without underlying disease, higher percentage of lymphocytes, higher percentage of basophils, greater number of large platelets, higher low-fluorescent reticulocyte ratio were found. These indicators might be protective factors, similar to CT-negative patients, they had better hematopoietic function and immunity (Adams et al. 2020). In addition, higher chloride, lower urea, lower creatinine, lower glucose, lower total bile acid, lower cystatin C, lower apolipoprotein B, lower hypersensitive CRP in blood were found in this patient group. Patients with hypertension, hyperlipidemia and diabetes account for

15/23 in patients with underlying diseases, this might be an explanation for the changes in the biochemical exams. We suggested that the biochemical differences between two groups are mainly from the underlying diseases.

There were three patients with repeatedly positive and negative results in nucleic acid tests in our sample. Their hospital stay was relatively long. In order to study their characteristics, we extracted the most prominent indicators in group comparisons and synthesized them into two index values. Index I can be seen as a sum of factors that were advantage for patients, and index J can be seen as a sum of factors that were disadvantage for patients. We then put these three patients in the sample distributions, and found that these three in the middle of the distributions of index I and J. We then concluded that patients with repeated positive and negative results in nucleic acid tests have both protective factors and risk factors. Therefore, their morbidity and symptoms were in a medium level, neither too serious nor easy to remove the virus.

In conclusion, CT-negative patients and patients without underlying diseases had mild symptoms, which were closely related to the number of lymphocytes and hematopoietic function. Blood routine testing was an good indicator of immunity. By comparing CT-negative and CT-positive patients, we found protective factors in blood:

lymphocytes, eosinophils number and %, basophils%, reticulocyte%, high fluorescence reticulocyte ratio, and reticulocyte absolute value. By comparing patients with underlying disease and without underlying disease, we found protective factors in blood: lymphocytes%, basophils%, large platelets, and low-fluorescent reticulocyte ratio. Regarding the biochemistry indicators, albumin/globulin, apolipoprotein and prealbumin can be considered as protective factors for patients without lung symptoms. Urea, glucose, total bile aicd, creatinine and hypersensitivity CRP can be considered as risk factors for patients with underlying diseases. However, for these patients, their biochemical changes were mainly from the underlying diseases. For patients with repeatedly negative and positive results in nucleic acid tests, they were at a medium level in terms of both protective and risk factors, which explained the mild symptoms and repeatedly negative and positive results in nucleic acid tests.

Abbreviations

ARDS= acute respiratory distress syndrome

COVID-19 = Coronavirus Disease 19

GGO = ground-glass opacity

MERS = Middle East respiratory syndrome

RT-PCR = reverse-transcription–polymerase-chain-reaction

SARS = severe acute respiratory syndrome

Declarations

Acknowledgements:

We thank the University of Anhui Medical University for giving ethical approval. We are also grateful for the laboratory personnel working in all targeted laboratories for giving ermission and participation in the data collection activities.

Authors’ contributions:

JL and LW conceived and designed the project. JL and YF collected the data. LW analyzed the data. LW and JL wrote the manuscript. HZ, JR and QZ searched the references and drew the figures. All authors read and approved the final manuscript.

Funding:

No fund was obtained for execution of the study.

Availability of data and materials:

The original data for this study is available from the corresponding authors upon request.

Ethics approval and consent to participate:

The study was ethically approved by Institutional Review Committee of the University of Anhui Medical University and official permission was obtained from all participating health facilities. Data from each facility was presented anonymously using code. All discordant results were also communicated to respective laboratories.

Consent for publication:

Not applicable.

Competing interests:

The authors declare that they have no competing interests.

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Tables

Table 1a: Group comparisons on blood routine (+: lung CT positive; -: lung CT negative)							
	Lymphocytes	Eosinophils	Eosinophils%	Basophils%	Reticulocyte absolute value	Reticulocyte percentage	High fluorescence reticulocyte ratio
Lung CT	-	-	-	-	-	-	-
Mean	1.73	0.12	2.09	0.40	58.59	1.40	1.34
SD	0.66	0.08	0.83	0.26	25.56	0.89	0.91
Lung CT	+	+	+	+	+	+	+
Mean	1.36	0.03	0.62	0.31	40.51	0.90	0.15
SD	0.50	0.04	0.52	0.18	16.71	0.40	0.41

Table 1b: Group comparisons on biochemistry (+: lung CT positive; -: lung CT negative)											
	Calcium	Creatinine	Urea Creatinine	Globulin	Albumin /Globulin	Creatine kinase	Lactate dehydrogenase	HDL/CHOL	Prealbumin	Apolipo-protein A1	SAA
Lung CT	-	-	-	-	-	-	-	-	-	-	-
Mean	2.32	52.61	0.08	22.99	1.92	46.00	178.91	28.58	211.72	1.18	45.46
SD	0.09	18.00	0.02	5.51	0.58	14.03	47.05	6.40	73.67	0.19	72.78
Lung CT	+	+	+	+	+	+	+	+	+	+	+
Mean	2.20	66.08	0.06	26.30	1.51	77.11	251.24	23.32	158.57	1.00	110.63
SD	0.15	17.62	0.02	2.95	0.23	51.92	76.92	5.76	55.04	0.21	69.04

Table 2a: Group comparisons on blood routine (0: without underlying diseases; 1: with underlying diseases)							
	Neutrophils	Lymphocytes%	Basophils%	Large platelet count	Immature reticulocyte ratio	Low fluorescent reticulocyte ratio	Medium fluoresce reticulocyte ratio
W/O Basic Disease	0	0	0	0	0	0	0
Mean	3.29	29.70	0.36	63.77	3.64	96.36	3.58
SD	1.58	11.03	0.20	16.36	2.74	2.74	2.55
Basic Disease	1	1	1	1	1	1	1
Mean	4.39	22.53	0.21	52.57	6.39	93.61	6.11
SD	2.13	8.72	0.10	17.04	3.65	3.65	3.22

Table 2b: Group comparisons on biochemistry (0: without underlying diseases; 1: with underlying diseases)								
	Chlorine	Urea	Creatinine	Glucose	Total Bile Acid	Cystatin C	Apolipoprotein B	Hyper -tivity CRP
W/O Basic Disease	0	0	0	0	0	0	0	0
Mean	104.96	3.53	58.17	5.48	3.09	0.88	0.73	11.35
SD	2.55	1.00	16.65	0.51	2.48	0.21	0.18	10.99
Basic Disease	1	1	1	1	1	1	1	1
Mean	102.79	4.99	75.64	7.84	4.69	1.16	0.85	30.56
SD	2.72	1.52	19.97	0.99	2.75	0.28	0.16	14.94

Figures

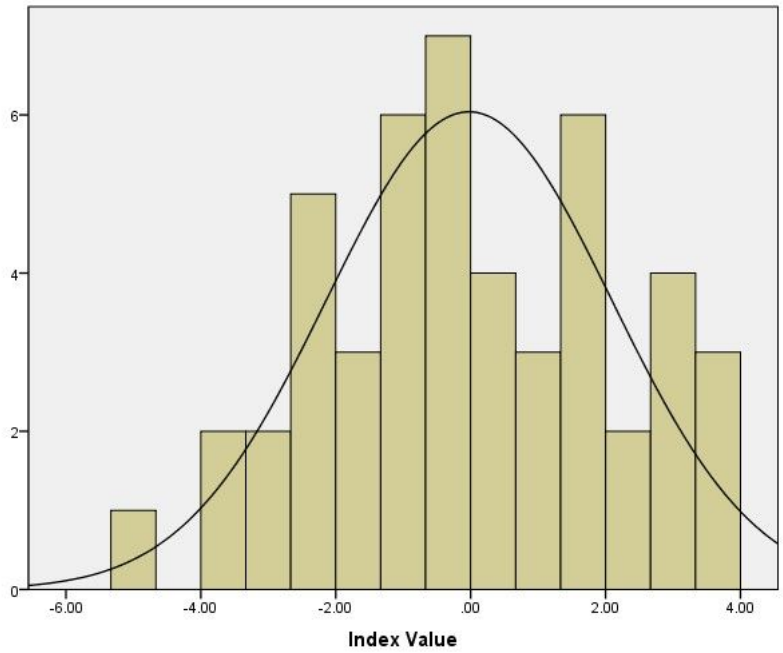

Figure 1

3b: The frequency of Index J (Patient A: -3.4; Patient B: 2.55; Patient C: -0.26)

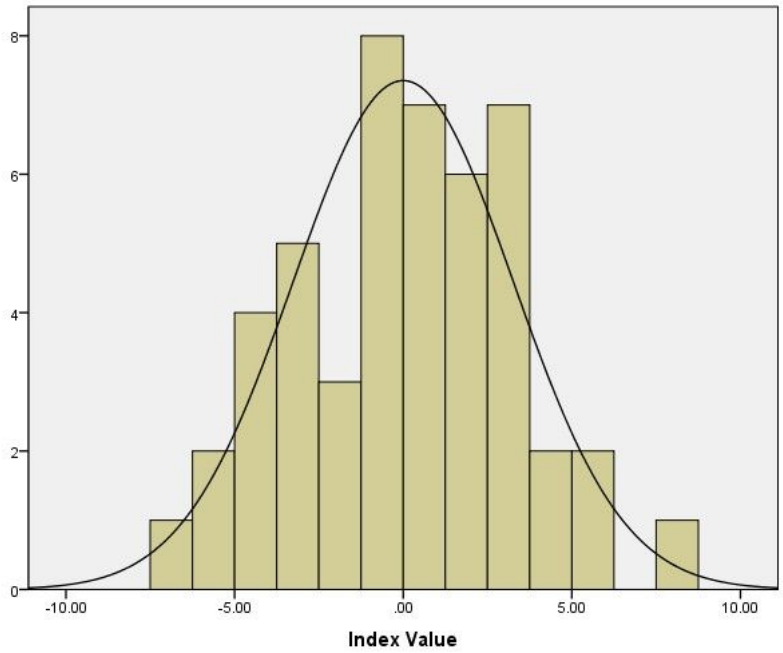

Figure 2

3a: The frequency of Index I (Patient A: 2.52; Patient B: -3.04; Patient C: 2.44)

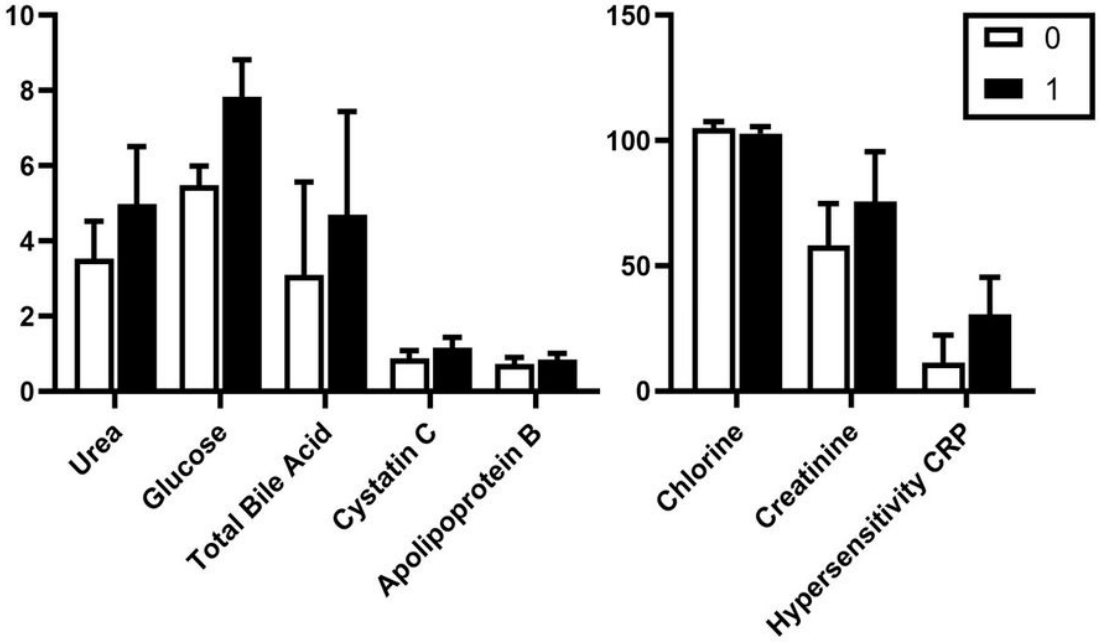

Figure 3

2b: Group comparisons on biochemistry (0: without underlying diseases; 1: with underlying diseases)

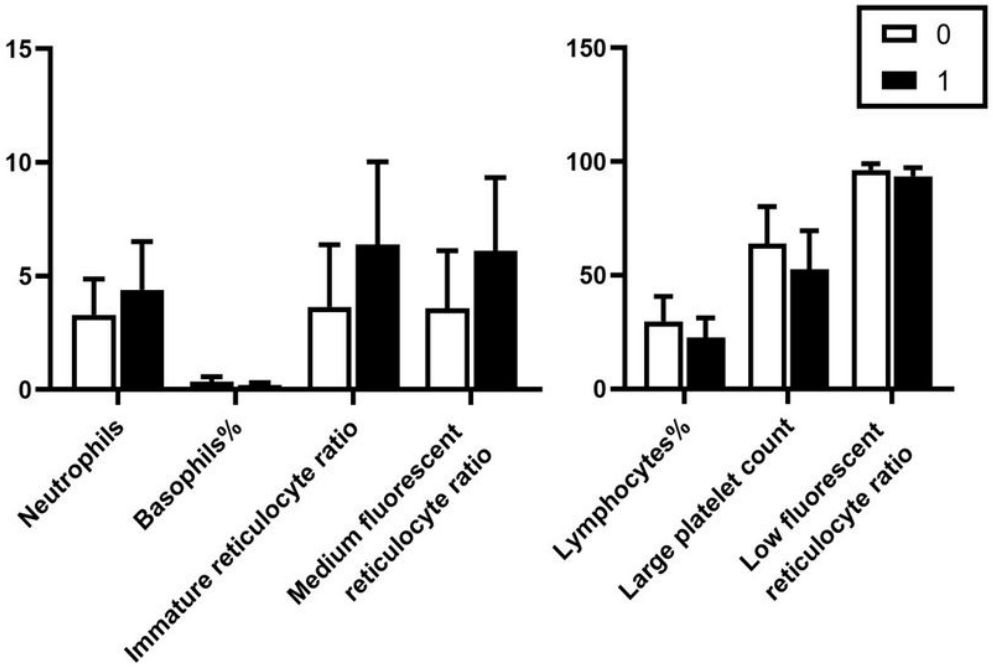

Figure 4

2a: Group comparisons on blood routine (0: without underlying diseases; 1: with underlying diseases)

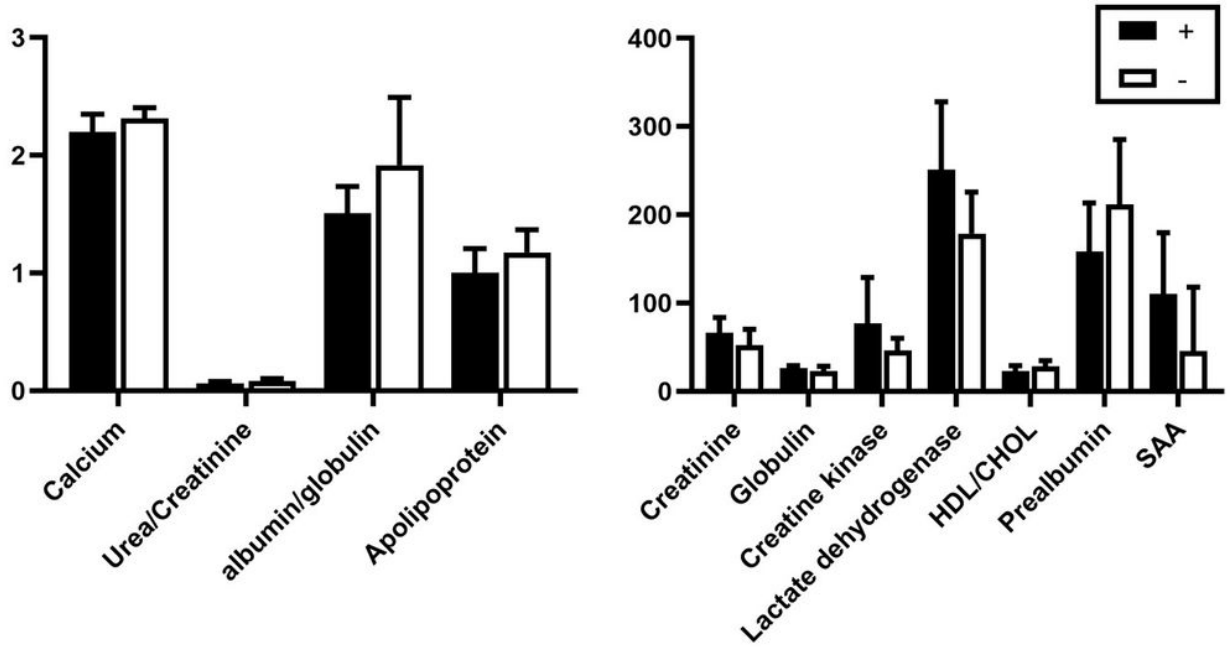

Figure 5

1b: Group comparisons on biochemistry (+: lung CT positive; -: lung CT negative)

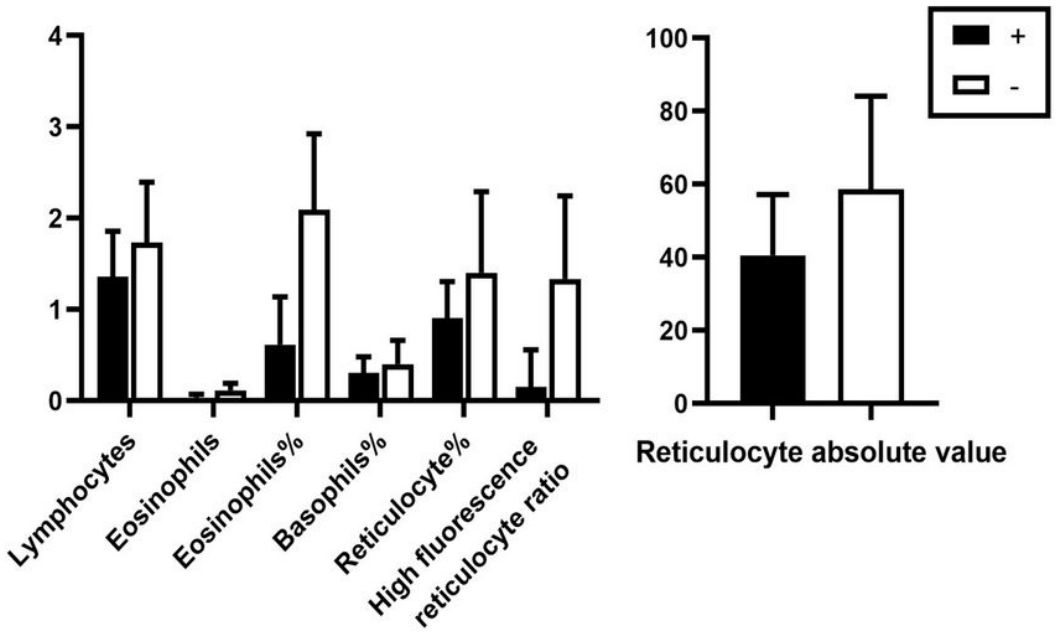

Figure 6

1a: Group comparisons on blood routine (+: lung CT positive; -: lung CT negative)