Dynamic Blood Tests Reveal Predicted Week of Death And Tricky Week For Surveillance In Severely Ill COVID-19 Patients

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Abstract

Background: Blood laboratory tests are the most reliable methods for the diagnosis and assessment of vital organs' functions and the body's response to infection. Herein, we compared the results of dynamic blood tests between the survivor and non-survivor group of patients with coronavirus disease 2019 (COVID-19) and aimed to determine the predicted and tricky week for death and surveillance.

Methods: The survivor and non-survivor groups were compared using biochemical blood tests, routine blood tests, and coagulation blood tests over four weeks of investigation.

Results: Blood urea nitrogen, creatinine, high-sensitivity C-reactive protein, total bile acid, neutrophil count, white blood cell count, D-dimer, fibrin and fibrinogen degradation product, and prothrombin time showed significantly higher levels in the non-survivor group than the survivor group. Only pre-albumin, eosinophil count, lymphocyte count, red blood cell count, platelet count, hemoglobin, and prothrombin activity tests were significantly higher in the survivor group than the non-survivor group. Generally, the third week of the non-survivor's group could be regarded as the predicted week for death based on all tests except for creatinine, pre-albumin, total bile acid, monocyte count, white blood cell count, and prothrombin activity. The tricky week in the non-survivor group was the second week in all tests except for pre-albumin, basophil count, eosinophil count, lymphocyte count, platelet count, D-dimer, and fibrin and fibrinogen degradation product.

Conclusions: Based on our study, specific attention should be given to some weeks with respect to their related tests as predicted or tricky for death or surveillance, respectively.

Background

In December 2019, the novel coronavirus disease 2019 (COVID-19) was first identified in Wuhan, China. The outbreak was eventually declared an international public health emergency in January 2020 and later a pandemic in March 2020 by the World Health Organization [1]. By October 2020, there were > 75 million confirmed cases of COVID-19 globally and > 1.6 million deaths [2]. COVID-19 infection is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This virus belongs to the Coronaviridae family and partially to SARS-CoV-2 and middle east respiratory syndrome-related coronavirus (MERS-CoV), that have caused previous epidemics in China and the Middle East, respectively [3].

Although nearly 80% of patients with COVID-19 show mild or moderate symptoms, those with severe and critical infection are more likely to be admitted to the intensive care unit (ICU) with worse prognosis [4]. The clinical and laboratory findings of COVID-19 patients may predict the severity in some cases. Elevated liver enzymes occur in a median of 15% [5] and up to 58% [6] of patients with COVID-19, and kidney damage was not uncommon [7]. Around 40% of hospitalized patients with COVID-19 in China were at a high risk of developing venous thromboembolism [8], had abnormal coagulation factors, and were associated with poor prognosis [9].

Although several laboratory findings on admission have been reported [10], the dynamic changes during the hospitalization period for both COVID-19 survivors and non-survivors have rarely been described. In addition, at specific time periods, some blood tests showed normal or abnormal records but without any previous

correlation to surveillance or death. In the present study, we investigated three groups of laboratory findings and their outcomes on surveillance and death with determination of specific weeks during treatment/admission. As the pandemic evolves, our findings may provide a scientific basis for death expectancy during four weeks of hospitalization for patients who survived or died during this this period.

Methods

Study design and participants

This retrospective observational study was conducted at Huanggang Central Hospital, Wuhan, China. In this study, COVID-19 was confirmed by real-time reverse-transcription polymerase chain reaction–based detection of SARS-CoV-2, and patients severely ill with COVID-19 were eligible for inclusion. The severity of COVID-19 was classified based on the Guidance for Coronavirus Disease 2019 (6th edition) released by the National Health Commission of China [11]. Briefly, the criteria for severe cases included dyspnea, respiratory rate ≥ 30 breaths per minute, blood oxygen saturation $\leq 93\%$, partial pressure of arterial oxygen to fraction of inspired oxygen ratio ≤ 300 , and/or lung infiltrates $> 50\%$ within 24–48 hour.

Severely ill COVID-19 patients were categorized into two groups: survivors (S) and non-survivors (NS) according to the final clinical outcomes of surveillance or death. Each group had 21 patients, and the laboratory tests were investigated over one month starting from the day of admission until the fourth week of hospitalization. These tests were categorized into three groups; biochemical blood tests, routine blood tests, and coagulation blood tests (Table 1).

Table 1
Dynamic blood tests for the four weeks of survivors and non-survivors groups.

Laboratory test	Week 1S ¹	Week 2S ²	Week 3S ³	Week 4S ⁴	Week 1NS ⁵	Week 2NS ⁶	Week 3NS ⁷	Week 4NS ⁸	Normal value
Biochemical blood tests									
Alpha-l-fucosidase (u/l)	55 ± 52	59 ± 57	68 ± 85	48 ± 45	35 ± 14	36 ± 15	33 ± 8.1	38 ± 15	< 40
Alanine aminotransferase (u/l)	29 ± 16	26 ± 18	48 ± 53	44 ± 29	31 ± 28	30 ± 22	49 ± 63	56 ± 87	29–33
Albumin (g/l)	31 ± 3.2	31 ± 3.2	31 ± 3.4	31 ± 2.2	29 ± 4.3	28 ± 3.0	28 ± 3.3	29 ± 4.0	34–54
Alkaline phosphatase (u/l)	50 ± 33	55 ± 34	52 ± 25	52 ± 17	71 ± 36	61 ± 22	68 ± 24	69 ± 23	44–147
Antigen test	1.2 ± 0.22	1.2 ± 0.29	1.2 ± 0.32	1.2 ± 0.21	1.1 ± 0.29	1.1 ± 0.22	1.1 ± 0.25	1.1 ± 0.31	
Aspartate aminotransferase (u/l)	31 ± 16	30 ± 15	33 ± 20	33 ± 25	46 ± 59	47 ± 57	56 ± 74	79 ± 181	5–40
Blood urea nitrogen (mmol/l)	2.9 ± 0.62	3.4 ± 0.83	3.5 ± 0.78	3.5 ± 0.80	4.5 ± 1.2	5.1 ± 1.9	7.4 ± 1.7	12 ± 5.8	2.5–7.1
Blood uric acid (µmol/L)	182 ± 53	193 ± 81	179 ± 71	232 ± 74	260 ± 141	186 ± 64	166 ± 69	227 ± 161	155–428
Creatinine (µmol/l)	62 ± 14	67 ± 21	53 ± 17	54 ± 18	84 ± 38	70 ± 19	72 ± 33	112 ± 99	60–110
Direct bilirubin (µmol/l)	5.6 ± 5.3	4.4 ± 2.1	6.1 ± 5.7	5.9 ± 5.8	7.0 ± 5.9	7.7 ± 6.8	11 ± 10	18 ± 38	< 5.1
Gamma-glutamyl transferase (u/l)	42 ± 53	47 ± 51	44 ± 50	32 ± 30	48 ± 50	34 ± 25	49 ± 28	46 ± 35	9–48
Globulin (g/l)	27 ± 3.0	27 ± 4.4	26 ± 4.3	27 ± 2.9	27 ± 4.2	27 ± 3.8	28 ± 4.5	28 ± 6.1	20–35
High sensitivity crp (mg/l)	3.7 ± 1.7	3.9 ± 1.7	2.9 ± 2.0	2.5 ± 2.0	4.8 ± 0.77	6.6 ± 4.4	13 ± 14	32 ± 43	< 10
Indirect bilirubin (µmol/l)	11 ± 5.9	8.8 ± 3.5	15 ± 10	13 ± 7.1	11 ± 9.2	13 ± 11	14 ± 10	20 ± 32	3.4–12.0
Pre albumin (mg/l)	183 ± 93	143 ± 72	192 ± 94	221 ± 113	126 ± 56	122 ± 31	159 ± 52	138 ± 54	150–360

1. First week of survivors group. 2. Second week of survivors group. 3. Third week of survivors group. 4. Fourth week of survivors group. 5. First week of non-survivors group. 6. Second week of non-survivors group. 7. Third week of non-survivors group. 8. Fourth week of non-survivors group.

Laboratory test	Week 1S ¹	Week 2S ²	Week 3S ³	Week 4S ⁴	Week 1NS ⁵	Week 2NS ⁶	Week 3NS ⁷	Week 4NS ⁸	Normal value
Total bile acid (μmol/l)	2.1 ± 0.71	2.2 ± 0.88	2.1 ± 0.76	2.4 ± 0.82	2.1 ± 0.60	2.9 ± 1.2	3.0 ± 1.1	5.3 ± 2.6	0–17
Total bilirubin (μmol/l)	18 ± 12	14 ± 8.3	21 ± 14	19 ± 12	18 ± 15	21 ± 17	26 ± 21	39 ± 70	1.71–20.5
Total protein (g/l)	57 ± 2.8	58 ± 3.6	57 ± 4.2	58 ± 2.6	57 ± 3.1	55 ± 4.1	55 ± 5.1	57 ± 6.9	60–83
Routine blood tests									
Basophil count (× 10 ⁹ /l)	0.022 ± 0.018	0.0060 ± 0.0086	0.016 ± 0.0086	0.021 ± 0.016	0.011 ± 0.0070	0.016 ± 0.019	0.016 ± 0.018	0.018 ± 0.013	0.02–0.05
Eosinophil count (× 10 ⁹ /l)	0.067 ± 0.14	0.022 ± 0.041	0.060 ± 0.048	0.11 ± 0.097	0.028 ± 0.046	0.019 ± 0.036	0.022 ± 0.035	0.046 ± 0.080	0.04–0.4
Haemoglobin (g/l)	138 ± 20	123 ± 16	118 ± 22	113 ± 17	101 ± 23	122 ± 27	107 ± 24	99 ± 18	115–150
Lymphocyte count (× 10 ⁹ /l)	1.5 ± 0.31	0.87 ± 0.34	1.1 ± 0.45	1.1 ± 0.36	0.71 ± 0.32	0.61 ± 0.27	0.49 ± 0.28	0.45 ± 0.30	1.0–4.0
Monocyte count (× 10 ⁹ /l)	0.64 ± 0.30	0.34 ± 0.20	0.47 ± 0.23	0.41 ± 0.14	0.80 ± 0.99	0.42 ± 0.30	0.49 ± 0.30	0.49 ± 0.41	0.2–0.8
Neutrophil count (× 10 ⁹ /l)	4.6 ± 2.7	3.2 ± 1.1	3.5 ± 0.84	2.7 ± 0.99	7.0 ± 4.6	4.1 ± 1.9	8.6 ± 6.7	11 ± 4.7	2.0–7.5
Platelet count (× 10 ⁹ /l)	194 ± 56	194 ± 77	255 ± 93	209 ± 71	166 ± 110	142 ± 87	142 ± 81	105 ± 80	150–450
Red blood cell count (× 10 ¹² /l)	4.6 ± 0.60	4.2 ± 0.61	4.0 ± 0.72	3.7 ± 0.62	3.5 ± 0.89	4.1 ± 1.1	3.6 ± 0.89	3.3 ± 0.78	3.8–6.5
White blood cell count (× 10 ⁹ /l)	6.9 ± 3.0	4.5 ± 1.3	5.1 ± 0.96	4.3 ± 1.0	8.6 ± 4.8	5.1 ± 1.9	8.5 ± 3.0	12 ± 4.8	4–11
Coagulation blood tests									
Activated partial thromboplastin time (sec)	30 ± 4.7	28 ± 3.5	26 ± 3.5	28 ± 6.0	29 ± 4.1	33 ± 13	28 ± 6.3	31 ± 7.6	21–35
Ddimer (ng/ml)	524 ± 812	1090 ± 2428	874 ± 1191	630 ± 780	2314 ± 4589	1513 ± 2505	3863 ± 3821	3493 ± 3003	< 500

1. First week of survivors group. 2. Second week of survivors group. 3. Third week of survivors group. 4. Fourth week of survivors group. 5. First week of non-survivors group. 6. Second week of non-survivors group. 7. Third week of non-survivors group. 8. Fourth week of non-survivors group.

Laboratory test	Week 1S ¹	Week 2S ²	Week 3S ³	Week 4S ⁴	Week 1NS ⁵	Week 2NS ⁶	Week 3NS ⁷	Week 4NS ⁸	Normal value
Fibrin and fibrinogen degradation product (µg/ml)	3.9 ± 6.2	9.4 ± 18	5.3 ± 7.3	4.4 ± 5.7	27 ± 49	18 ± 40	34 ± 38	29 ± 27	< 10
Fibrinogen (g/l)	4.2 ± 1.7	4.6 ± 2.2	4.0 ± 1.2	3.8 ± 0.97	4.6 ± 1.3	4.8 ± 1.4	4.4 ± 1.5	4.5 ± 1.5	1.5–4.5
Prothrombin activity (%)	114 ± 26	111 ± 22	113 ± 18	112 ± 21	111 ± 24	105 ± 24	88 ± 18	74 ± 20	75–135
Prothrombin time (sec)	11 ± 0.62	11 ± 0.81	11 ± 0.87	11 ± 0.70	11 ± 0.53	12 ± 0.80	13 ± 1.0	14 ± 1.7	11.0–12.5
Thrombin time (sec)	14 ± 2.4	14 ± 2.9	15 ± 2.6	14 ± 1.9	14 ± 1.5	14 ± 0.99	15 ± 2.1	15 ± 3.6	12–14
1. First week of survivors group. 2. Second week of survivors group. 3. Third week of survivors group. 4. Fourth week of survivors group. 5. First week of non-survivors group. 6. Second week of non-survivors group. 7. Third week of non-survivors group. 8. Fourth week of non-survivors group.									

Data collection

A team of experienced physicians reviewed and analyzed the electronic medical and nursing records of COVID-19 patients to collect information on demographics, exposure history, underlying comorbidities, and laboratory blood tests.

To determine the major clinical features of deterioration in COVID-19 patients, we compared the laboratory findings between survivors and non-survivors from the first to the fourth week after the onset of illness. The median values of laboratory parameters in each week were considered as representative values of that week for each patient. Each week with normal or abnormal test records was regarded as the week for surveillance or death prediction, respectively (Table 1). If the test record was normal in the non-survivors' group, that week was regarded as the tricky week for surveillance; whereas, if the test record was abnormal in the survivors' group, that week was regarded as the tricky week for death (Table 2).

Table 2
Significant results of blood tests with predictable and tricky weeks for surveillance and death.

Laboratory test	Predicted week for surveillance/mortality	Tricky week for mortality/surveillance
Biochemical blood tests		
Blood urea nitrogen	Week 1S, 2S, 3S, 4S/Week 3NS, 4NS	-/Week 1NS, 2NS
Creatinine	Week 1S, 2S/Week 1NS, 4NS	Week 3S, 4S/Week 2NS, 3NS
High sensitivity CRP	Week 1S, 2S, 3S, 4S/Week 3NS, 4NS	-/Week 1NS, 2NS
Pre albumin	Week 1S, 3S, 4S/week 1NS, 2NS, 4NS	Week 2S/week 3NS
Total bile acid	Week 1S, 2S, 3S, 4S/-	-/ week 1NS, 2NS, 3NS, 4NS
Routine blood tests		
Basophil count	Week1S, 4S/week 1NS, 2NS, 3NS, 4NS	Week 2S, 3S/-
Eosinophil count	Week 1S, S3, 4S/week 1NS, 2NS. 3NS	Week 2S/week 4NS
Haemoglobin	Week 1S, 2S, 3S/week 1NS, 3NS, 4NS	Week 4S/week 2NS
Lymphocyte count	Week1S, 3S, 4S/week 1NS, 2NS, 3NS, 4NS	Week 2S/-
Monocyte count	Week 1S, 2S, 3S, 4S/-	-/week 1NS, 2NS, 3NS, 4NS
Neutrophil count	Week 1S, 2S, 3S, 4S/week 3NS,4NS	-/week 1NS, 2NS
Platelet count	Week 1S, 2S, 3S, 4S/week 2NS, 3NS, 4NS	-/week 1NS
Red blood cell count	Week 1S, 2S, 3S/week 1NS, 3NS, 4NS	Week 4S/week 2NS
White blood cell count	Week 1S, 2S, 3S, 4S/week 4NS	-/week 1NS, 2NS, 3NS
Coagulation blood tests		
D-dimer	-/week 1NS, 2NS, 3NS, 4NS	Week 1S, 2S, 3S, 4S/-
Fibrin and fibrinogen degradation product	Week 1S, 2S, 3S, 4S/week 1NS, 2NS, 3NS, 4NS	-/-
Prothrombin activity	Week 1S, 2S, 3S, 4S/week 4NS	-/week 1NS, 2NS, 3NS
Prothrombin time	Week 1S, 2S, 3S, 4S/week 3NS, 4NS	-/week 1NS, 2NS

Study approval

This study was approved by the Research Ethics Committee of Huanggang Central Hospital (HGY-2020-010). The requirement for informed consent was waived by the Ethics Committee on account of the retrospective nature of this study. All methods were performed in accordance with the the protocol of the World Medical Association Declaration of Helsinki.

Statistical analysis

Data were retrieved to an Excel Worksheet and then analyzed using Graph Pad (5.04, La Jolla, CA USA) for Windows to generate group comparison. Each group of survivors and non-survivors contained an additional four subgroups representing the first, second, third, and forth week of hospitalization. One-way ANOVA was generated using Box and Whisker/Tukey appearance. The Bonferroni multiple comparison test was used for inter- and intragroup comparisons of survivors and non-survivors. $P \leq 0.05$ was considered to indicate statistical significance.

Results

Different records between weeks in the survivor and non-survivor groups

Biochemical blood tests

The biochemical profile was represented by 18 tests. The non-significant values between/within survivors and non-survivors are shown in supplementary figure 1. Blood urea nitrogen, creatinine, high-sensitivity C-reactive protein (CRP), pre-albumin, and total bile acid tests showed several significant differences within and between each group (Figure 1).

Blood urea nitrogen

In the blood urea nitrogen test, no significant difference was found within the survivor group, while several differences were reported within the non-survivor group and between both the survivor and non-survivor groups. Highly significant differences were found between week 4NS group and week 3NS, week 2NS, week 1NS, week 4S, week 3S, week 2S, and week 1S ($P \leq 0.001$). Other significant differences were found between week 3NS and week 1NS ($P \leq 0.01$), and between week 3NS and week 4S, week 3S, week 2S, and week 1S ($P \leq 0.001$) (Figure 1A).

Creatinine

No significant difference was found within the survivor group. However, significant differences were found between week 4NS and week 2NS and week 2S ($P \leq 0.05$); between week 4NS and week 4S and week 3S; ($P \leq 0.001$), and between week 4NS and week 1S ($P \leq 0.01$). (Fig. 1B)

High-sensitivity CRP

No significant difference was found within the survivor group, while a significant difference was found between week 4NS and week 3NS within the non-survivor group ($P \leq 0.01$). A significant increase in high-sensitivity CRP was observed at week 4NS compared to week 2NS, week 1NS, week 4S, week 3S, week 2S, and week 1S ($P \leq 0.001$) (Fig. 1C).

Pre-albumin

In the survivors' group, pre-albumin was significantly high in week 4S compared to week 2S ($P \leq 0.05$). On the other hand, a significant increase was found in week 4S in comparison to week 1NS ($P \leq 0.01$), week 2NS ($P \leq 0.001$), and week 4NS ($P \leq 0.05$) (Fig. 1D).

Total bile acid

Within the survivors' group, no significant difference was found. The highest value was recorded in week 4NS with highly significant differences in relation to week 3NS, week 2NS, week 1NS, week 4S, week 3S, week 2S, and week 1S ($P \leq 0.001$) (Fig. 1E).

Routine blood tests

The routine blood tests were represented by nine tests. All tests showed several significant inter- and intragroup differences in each group (Fig. 2).

Basophil count

The highest value of basophil cells was recorded in week 1S and week 4S. Significant differences were found between week 4S and week 2S ($P \leq 0.05$) and between week 2S and week 1S ($P \leq 0.01$) (Fig. 2A).

Eosinophil count

In the survivors' group, a significantly higher value was found in week 4S than week 2S ($P \leq 0.01$). However, week 4S showed higher values than week 2NS, week 3NS ($P \leq 0.01$), and week 1NS in the non-survivors group ($P \leq 0.05$) (Fig. 2B).

Lymphocyte count

Significant differences were found within and between the survivor and non-survivor groups. The highest record was found in week 1S. Week 2S was significantly higher than week 3NS and week 4NS ($P \leq 0.01$), while week 3S was significantly higher than week 1NS ($P \leq 0.01$), week 2NS, week 3NS, and week 4NS ($P \leq 0.001$). Additionally, week 4S was higher than week 1NS ($P \leq 0.01$), week 2NS, week 3NS, and week 4NS ($P \leq 0.001$) (Fig. 2C).

Monocyte count

The highest monocyte count was found in week 1S and week 1NS, while significant differences were found only between week 1NS and week 2S ($P \leq 0.05$) (Fig. 2D).

Neutrophil count

The neutrophil count was higher in the non-survivor group especially in week 1NS, week 3NS, and week 4NS (Fig. 2E). Significant high neutrophils count was found in week 4NS in comparison to week 2NS ($P \leq 0.01$), week 1NS ($P \leq 0.05$), week 4S, week 3S, week 2S, and week 1S ($P \leq 0.001$). Week 3NS was significantly higher than

(week 2NS, week 4S, week 3S, and week 2S) ($P \leq 0.001$), and week 1S ($P \leq 0.05$). Week 1NS was higher in comparison to week 4S ($P \leq 0.01$), week 3S, and week 2S ($P \leq 0.05$) (Fig. 2E).

White blood cell count

No significant difference was found within the survivors group. The highest level of white blood cell count was detected in week 4NS and week 1NS with significant differences between them ($P \leq 0.01$). A significant difference was also found between week 4NS and week 3NS ($P \leq 0.01$). Highly significant differences were found between week 4NS and week 2NS, week 4S, week 3S, week 2S, and week 1S ($P \leq 0.001$). Higher levels of white blood cells were detected in week 3NS than week 2NS, week 3S ($P \leq 0.01$), week 4S, and week 2S ($P \leq 0.001$). The differences between week 1NS and week 2NS and between week 1NS and week 4S, week 2S ($P \leq 0.001$), and week 3S ($P \leq 0.01$) were significant (Fig. 2F).

Red blood cell count

Significant intragroup differences were found in the survivor and non-survivor groups between week 1S and week 4S ($P \leq 0.01$), week 1NS, week 4NS ($P \leq 0.001$), and week 3NS ($P \leq 0.01$). Another significant difference was found between week 2S and week 4NS ($P \leq 0.05$) (Fig. 2G).

Platelet count

Higher platelet counts were observed at week 1S and week 3S. Significant differences were found between week 1S and week 4NS ($P \leq 0.01$), and between week 2S and week 4NS ($P \leq 0.01$). Other significant differences were observed between week 3S and week 1NS ($P \leq 0.01$), week 2NS, week 3NS, week 4NS ($P \leq 0.001$) and between week 4S and week 4NS ($P \leq 0.001$) (Fig. 2H).

Hemoglobin

The highest level was recorded for week 1S with significant differences compared to week 4S ($P \leq 0.01$), week 1NS, week 3NS, and week 4NS ($P \leq 0.001$). Week 2S showed significantly higher hemoglobin levels than week 1NS ($P \leq 0.05$) and week 4NS ($P \leq 0.01$). Other significant differences were observed between week 1NS and week 2NS and between week 3NS and week 4NS ($P \leq 0.05$) (Fig. 2I).

Coagulation blood tests

Seven blood coagulation tests were dynamically tested over the four weeks among both survivors and non-survivors. Activated partial thromboplastin time, fibrinogen, and thrombin time did not show any significant difference between and within the survivors and non-survivors (Supp. Fig. 2). On the other hand, D-dimer, fibrin and fibrinogen degradation products, prothrombin activity, and prothrombin time showed significant differences within and between groups (Fig. 3).

D-dimer

The highest value of D-dimer was recorded in week 3NS with significant differences compared to week 1S ($P \leq 0.001$), week 2S ($P \leq 0.01$), week 3S ($P \leq 0.01$), week 4S ($P \leq 0.001$). Week 4NS showed significant high records compared to week 1S ($P \leq 0.01$), week 2S, week 3S ($P \leq 0.05$), and week 4S ($P \leq 0.01$) (Fig. 3A).

Fibrin and fibrinogen degradation products

These results were higher in week 3NS than week 4S, week 3S, and week 1S ($P \leq 0.05$) (Fig. 3B).

Prothrombin activity

No significant differences were observed within the survivors group. On the other hand, significantly low prothrombin activity was found in week 4NS compared to week 4S, week 3S, week 2S, and week 1S ($P \leq 0.001$). Low activity was also found in week 3NS compared to week 4S, week 2S ($P \leq 0.05$), week 3S, and week 4S ($P \leq 0.01$) (Fig. 3C).

Prothrombin time

No significant differences were found within the survivors group. In the non-survivor group, significant differences were observed in week 4NS compared to week 3NS ($P \leq 0.01$), week 2NS, and week 1NS ($P \leq 0.001$) and in week 3NS compared to week 1NS ($P \leq 0.001$). Higher values were also observed in week 4NS than week 4S, week 3S, week 2S, and week 1S ($P \leq 0.001$). Other high values were found in week 3NS compared to week 4S, week 3S, week 2S, and week 1S ($P \leq 0.001$). Finally, only two significant differences were found in week 2NS compared to week 4S and week 3S ($P \leq 0.01$) (Fig. 3D).

Predicted or tricky weeks for surveillance and death

Predicted or tricky weeks as blood test biomarkers for surveillance and death have been recorded (Table 2). In our results and discussion, we will be focusing on the early predicted weeks for death (week 1NS, week 2NS, or week 3NS) and accordingly, the tricky weeks for surveillance for the clinicians to consider them as risk factors with time specification related to their underlining condition.

Biochemical blood tests

In the non-survivor group, the predicted weeks for death were likely week 3NS with respect to both blood urea nitrogen and high-sensitivity CRP, while for creatinine and pre-albumin, week 1NS and both week 1NS and week 2NS, respectively, were the predicted weeks for death. Accordingly, the tricky weeks for surveillance in blood urea nitrogen and high-sensitivity CRP were weeks 1NS and 2NS. Both week 2NS and week 3NS could be regarded as tricky weeks for surveillance in creatinine, while only week 3NS in the pre-albumin test may be the tricky week. All the investigated weeks for total bile acid in the non-survivor group could be regarded as tricky weeks for surveillance (Table 2).

Routine blood tests

Within the non-survivor group, all weeks for basophil count and lymphocyte counts could be regarded as predicted weeks for death, while for eosinophil count and hemoglobin test, only the first three weeks and the first and third weeks, respectively, could be regarded as the predicted weeks for death. Neutrophil count, platelet count, and red blood cell count shared the 3NS as predicted week for death, while the additional week for prediction was week 2NS and 1NS for platelet count and red blood cell count, respectively. On the other hand, the early tricky week for surveillance was week 2NS for the hemoglobin test and red blood cell count, all the

investigated weeks for monocyte count, the first two weeks for neutrophil count, the first three weeks for white blood cell count, and only week 1NS and 2NS for platelet count and red blood cell count, respectively (Table 2).

Coagulation blood tests

For D-dimer and fibrin and fibrinogen degradation product tests, all the weeks in the non-survivor group could be the predicted weeks for death, while only week 3NS may be the predicted week for death in prothrombin time. Conversely, week 1NS, week 2NS, and week 3NS can be regarded as the tricky weeks for surveillance in prothrombin activity, while only week 1NS and week 2NS can be the tricky weeks for surveillance in prothrombin time (Table 2).

Discussion

Different records between weeks in the survivor and non-survivors' groups

Biochemical blood tests

In the current study, several biochemical tests were conducted for both survivors and non-survivors of COVID-19 over the hospitalization period of four weeks. The evaluation of kidney function could be tested using different tests including blood urea nitrogen and creatinine. Blood urea nitrogen levels were within the normal range for the entire 4 weeks in the survivor group, while it started to increase from the third week and continued to increase up to the fourth week in the non-survivor group, with significantly higher values compared to the other weeks. Other studies showed that blood urea nitrogen was regarded as one of the predictive tests for surveillance with significant elevation in the non-survivor group [12, 13]. In addition to blood urea nitrogen, creatinine was not found to be different between severe and moderate cases of COVID-19 [13] when measured during the first weeks of infection. Our results showed that creatinine was obviously and significantly higher in the fourth week of the non-survivor group than week 2NS and week 1S, week 2S, week 3S, and week 4S.

In inflammation, high-sensitivity CRP is regarded as one of the most common and accessible tests. In the third and fourth week in the non-survivor group, high-sensitivity CRP was obviously elevated when compared to others. Wang et al. found that even in the early stages of severe and critical COVID-19, CRP was higher than the normal level and positively correlated to the lung lesion [14] but without declination in critically ill patients in the latter period of hospitalization [15]. Along with that, pre-albumin is regarded as the precursor of different inflammatory proteins including acute phase protein [16]. Luo et al. predicted a worse outcome of COVID-19 in patients with low level of pre-albumin on admission [17]. During the whole period of hospitalization of COVID-19 patients, a significantly low level of pre-albumin was recorded in the first, second, and fourth week in the non-survivor group, when compared to the second and fourth week in the survivor group. In COVID-19 patients, we found that total bile acid was significantly higher in week 4NS than all other weeks. The normal level of total bile acid in blood should range between 0 and 17 $\mu\text{mol/L}$ [18], while in COVID-19 patients it was higher than the normal value, especially in week 4NS.

Routine blood tests

All the routine blood tests showed significant variance within/between the survivors and non-survivors. Basophil count was reported to be normal and relatively higher at the early and late stage of infection in the survivor group than all weeks in the non-survivor group. A prediction of severity was concluded with a lower

than normal level at the early stage of infection and even in comparison with the control group [19]. Eosinopenia ($< 0.02 \times 10^9/L$) which has been reported at the admission time of fatal cases of COVID-19, was regarded as a risk factor [20]. We reported a normal eosinophil count at week 1S and despite its declination during week 1S and week 2S, elevation was noticed at week 3S promising a good prognosis. Liu et al. noticed that the antiviral treatment of COVID-19 patients had improved eosinopenia at the late stage before discharge [21]. Normal lymphocyte levels at the week of admission were regarded as a good prognostic marker for the following weeks [22]. A normal level of lymphocyte count at week 1S was reported despite its declination at only week 2S, while all four weeks in the non-survivor group recorded less than the normal level. In the survivors group, the monocyte count was within the normal level during the hospitalization period, while it was on its highest normal level at week 1NS suggesting a bad prognosis or severe disease [23]. In addition, for neutrophil count, the survivors group showed normal levels throughout the four weeks, while week 1NS showed a significantly higher level than week 2S, week 3S, and week 4S. This high value decreased in week 2NS but again elevated in week 3NS and week 4NS to be significantly higher than other weeks in the survivors and non-survivor groups. The comparison followed the same pattern of significantly higher values of neutrophil count in the non-survivors than survivors but in general and without any week specificity [24]. The latter study also showed a significantly high level of white blood cell count in the non-survivors than survivors [24]. Despite that, all the weeks of both groups showed normal level of white blood cell count except week 4NS, which showed a significantly high level in comparison to all other weeks.

Among the red blood cell and platelet counts and hemoglobin level, we found that red blood cell count during week 1S was within the normal range but significantly higher than week 1NS. This meant that a slight abnormal level in week 1NS may be a predictive risk factor for COVID-19 patients despite the elevation in week 2NS; however, it returned to lower than normal levels in week 3NS and week 4NS. Yuan et al. found that red blood cell count was significantly lower in critically ill COVID-19 patients than in regular COVID-19 patients, confirming that the red blood cell count may play an important prognostic marker for worse prognosis due to insufficient oxygen transportation [25]. In relation to the impact of cytokine storm to thrombocytopenia and low platelet count [26], the results of Mehta et al. were in accordance with ours, in that the decline in platelet count started at week 1NS followed by week 2NS/3NS and week 4NS. For hemoglobin, other studies did not find significant differences between survivors and non-survivors [24, 27], while our study provide an insight from week 1S and week 1NS that either surveillance or death are expected, respectively, as the week 1S value was significantly higher than that of week 1NS.

Coagulation blood tests

D-dimer has extensively been studied for its relationship to COVID-19 infection and as a biomarker for disease severity [28–31], especially in the post admission stage [32]. In the current study, all weeks in both the survivor and non-survivor groups showed an elevated level of D-dimer, but significantly higher values were seen in week 3NS and week 4NS compared to other weeks. Fibrin and fibrinogen degradation products during the whole period of hospitalization in the survivor group were within normal levels, while they were significantly elevated and exceeded normal levels in the non-survivor group in all weeks of hospitalization.

A meta-analysis was performed on 17 studies to determine the relation of high abnormal levels of fibrin and fibrinogen degradation products at admission to poor outcome [33]. For prothrombin activity, no obvious change was observed for all the weeks in the survivor group, as it ranged between 111% and 114%. The level

was within normal levels in week 1NS, week 2NS, and week 3NS, but in week 4NS, it declined to below the lowest normal level. In accordance with this finding, Luo et al. reported a significantly low level of prothrombin activity in the non-survivors group [34]. Although prothrombin time was recorded to be normal and steady on 11 second, it showed a gradual increase in the non-survivors' group starting from week 2NS, revealing it as a poor prognostic marker. A significant prolongation in prothrombin time was recorded in non-survivors compared to survivors [9, 34].

Predicted or tricky weeks for surveillance and death

Biochemical blood tests

For the biochemical tests, we reported several predicted weeks for death. In our study, week 3NS could be a predicted week for death in blood urea nitrogen test. In another study and from the third week, the survival curve declined to 50% when the blood urea nitrogen exceeded 4.6 mmol/L with high specificity, sensitivity, and a strong predictive value for mortality [35]. A significantly high value of creatinine at admission was reported with a progressive increase in the non-survivors group until death [36], revealing that early attention is important for this test. High-sensitivity CRP was recorded to be significantly higher at the week of death compared to week of admission, but in this study, the time-interval between admission and death was only 12 days [37]. The highest records for aggravation of symptoms and its relation to CRP level started from the third week in severe cases of COVID-19 patients [38] expecting that week 3NS could be an early predicted week for death in the non-survivor group. In our study, we predicted that week 1NS and week 2NS for pre-albumin test could be an indicator for death, while Luo et al. predicted the admission week as a predictor for death with significantly low levels in non-survivors [39].

Conversely, the range of blood urea nitrogen [12] and high-sensitivity CRP were different according to each laboratory and performed procedure. Wang et al. considered the cut-off value of CRP to be 26 mg/L [38] and have considered it as a risk factor for severity, specifically after the 10th day of infection. While in our study, blood urea nitrogen and high-sensitivity CRP remained at the normal level during the first two weeks, which could be the tricky weeks for surveillance. As expected, there may be a change in the creatinine level towards normal starting from the 18th day to the 27th day of admission [40]. In the present study, week 3NS could be expected as a tricky week for surveillance in the pre-albumin test, but until now no published data supports this suggestion. Collectively, all four weeks of total bile acid test in the non-survivors group could be tricky weeks for surveillance, or in other words, cannot be a risk factor for death of COVID-19 patients. This test has also been recorded to be within the normal range at least at the time of admission [41].

Routine blood tests

In our study, the most obvious predicted weeks for death are represented by the whole period of hospitalization in the non-survivors group. Ferrari et al. reported the same in basophil count and lymphocyte count [42] with a significant association with severe COVID-19 patients. Eosinophil count at week 1NS, week 2NS, and week 3NS could be the predicted weeks for death or accordingly in another study as a valid predictive marker for intensive care unit transfer for elderly COVID-19 patients [43]. Hemoglobin significantly correlated to the severity at admission [44], while in our study, it has been correlated to death. Here, neutrophilia was reported at the third week of infection and as one of the risk factors associated with death in accordance with Wang et al. [36].

Lower than normal platelet counts started from week 2NS and later, which was clearly indicated by Zhao et al. to be a significant biomarker for poor prognosis and death [45]. Our study reported lower than the normal level for the red blood cell count in the first and third week in non-survivor group expecting an early predicted week for death. Yuan et al. also reported a significant lower red blood cell count in severe and critically ill than in the regular group but without specification to which week the record was reported [46].

Some blood tests should be considered as tricky tests in specific time periods. Week 2NS may exhibit normal hemoglobin levels, but it was a poor prognostic marker as indicated by Lippi and Mattiuzzi in which the continuous decrease in hemoglobin is a risk factor for death [44]. Zhao et al. reported a significant increase in neutrophil count at the admission (first week) in non-survivors compared to survivors, which was the same as in our study. Despite this similarity, in both ours and Zhao et al's studies [45], the first week of the non-survivor group demonstrated that the neutrophil count was within the normal level, taking into consideration that this normal level may still be a tricky sign or tricky week for surveillance. The same explanation may be valid for the platelet count [45]. The red blood cell count in our study was within the normal level in the second week of non-survivors group taking into consideration that this week could be a tricky week for surveillance. To our knowledge, no previous study has specified this trickiness before. The first three weeks in the non-survivor group could be the tricky weeks for death for the white blood cell count as it is within the normal range. Yuan et al. reported this test to be within the normal range at admission in regular COVID-19 patients, while it was significantly high in severe and critically ill COVID-19 patients [46]. Surprisingly, we found that the monocyte count from week 1NS to week 4NS was still within the normal range, indicating the strongest tricky sign for death, while Fan et al. demonstrated a lower monocyte count in severe COVID-19 patients compared to non-severe ones [47].

Coagulation blood tests

In the non-survivor group and for D-dimer test and fibrin and fibrinogen degradation products test, we found that week 1NS to week 4NS were the predicted weeks for death. Accordingly, studies recorded a significantly high level of D-dimer [48] and fibrin and fibrinogen degradation products [34] correlating them to poor prognosis in severe COVID-19 patients. We recorded several significant increases in prothrombin time in week 3NS compared to other weeks, while Tang et al. recorded a significantly high correlation of prothrombin time to mortality on the 28th day [49].

On the other hand, the first two weeks and the first three weeks in the non-survivor group were regarded as tricky weeks for surveillance in prothrombin time and prothrombin activity tests, respectively. Similar to our results, Luo et al. predicted that the prothrombin time at admission was a predictor for mortality but still at the normal level [34], while Tang et al. reported abnormally high prothrombin time at admission and within the whole period of hospitalization in the non-survivors group [9]. Week 1NS, week 2NS, and week 3NS were found to be the tricky week for surveillance in prothrombin activity, which has been also reported that by another study that this test was related to mortality in non-survivors despite its normal level [50].

Conclusion

Dynamic blood tests in COVID-19 patients reveal important indicators of the physiological function of vital organs, in addition to providing a focused attention on a specific time period during hospitalization. The

significant differences between weeks in survivors and non-survivors, and whether they are within or outside the normal range, could be helpful in another interpretation for surveillance or death as predicted or tricky weeks.

Abbreviations

COVID-19: Coronavirus disease 2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; MERS: Middle East respiratory syndrome; S: Survivors; NS: Non-survivors; CRP: C-reactive protein

Declarations

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Author contributions

Shiyong Li, Mohammed A Alsaegh, and Rao Sun designed the research and the research methods, analyzed the results, and made critical revisions to the paper; Liping Jia, Alaa M Altaie, and Quanshui Hao analyzed the results and made significant contributions to the initial manuscript draft; Fang Luo, Ailin Luo, Jing Lu, Xian Yang, Changfeng Wang, Yaohua Wu, Zhaoxia Jin, Hui Zhang, Fan Zhou, and Yaqi Zhang helped with patient recruitment and data collection and assisted in data analysis.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding authors on reasonable request.

Ethics approval and consent to participate

All methods were performed in accordance with the protocol of the World Medical Association Declaration of Helsinki. The study involving human participants were reviewed and approved by the Research Ethics Committee of Huanggang Central Hospital (HGY-2020-010). The requirement for informed consent was waived by the Research Ethics Committee of Huanggang Central Hospital.

Consent for publication

No individual participant data is reported that would require consent to publish from the participant (or legal parent or guardian for children).

Competing interests

The authors declare that they have no competing interests.

Supplementary information

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Figures

Figure 1

Significant differences in biochemical blood tests. (A) Blood urea nitrogen, (B) Creatinine, (C) High-sensitivity CRP, (D) Pre-albumin, and (E) Total bile acid.

Figure 2

Significant differences in routine blood tests. (A) Basophil count, (B) Eosinophil count, (C) Lymphocyte count, (D) Monocyte count, (E) Neutrophil count, (F) White blood cell count, (G) Red blood cell count, (H) Platelet count, and (I) Hemoglobin.

Figure 3

Significant differences in coagulation blood tests. (A) D-dimer, (B) Fibrin and fibrinogen degradation products, (C) Prothrombin activity, and (D) Prothrombin time.

Supplementary Files

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