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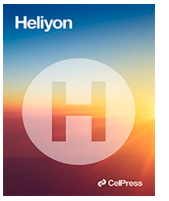

Research article

Prolonged lymphopenia and prognoses among inpatients with different respiratory virus infections: A retrospective cohort study

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ABSTRACT

Background: Lymphopenia is common in respiratory viral infection. However, no studies elucidated the impact of prolonged lymphopenia on worse outcome in the way of quantitative risk.
Methods: Adult patients with laboratory-confirmed respiratory virus infection (influenza, SARS-CoV-2, and other viruses) between January 1st, 2016, and February 1st, 2023 were enrolled in this retrospective cohort study. Serial data of laboratory examination during hospitalization were acquired. The primary outcome was in-hospital all-cause death, and all information was obtained from the electronic medical records system. Legendre orthogonal polynomials (LOP), restricted cubic splines, and multivariable logistic regression were performed.
Results: Finally, 2388 inpatients were involved in this study, including 436 patients with influenza, 1397 with SARS-CoV-2, and 319 with other respiratory virus infections. After being adjusted for age, corticosteroids, chronic kidney disease, chronic respiratory disease, cardiovascular disease, lymphopenia on admission and length of hospital stay, prolonged lymphopenia was significantly associated with death in influenza (OR 7.20, 95 % CI 2.27–22.77, $p = 0.0008$ for lasting for 3–7 days; OR 17.80, 95 % CI 5.21–60.82, $p < 0.0001$ for lasting for more than 7 days)

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and SARS-CoV-2 (OR 3.07, 95 % CI 1.89–5.01, $p < 0.0001$ for lasting for 3–7 days; OR 6.28, 95 % CI 3.53–11.18, $p < 0.0001$ for lasting for more than 7 days), compared with a transient lymphopenia of 1–2 days, while no significant association was found in other respiratory viruses. Prolonged lymphopenia was also associated with multi-organ damage in influenza and SARS-CoV-2 infections.

Conclusions: Prolonged lymphopenia was significantly associated with worse clinical prognoses in influenza and SARS-CoV-2 infections, but not in other respiratory virus infections.

1. Introduction

Influenza virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and other respiratory viruses, including respiratory syncytial virus (RSV), parainfluenza virus (PIV), human rhinovirus, coronavirus, human metapneumovirus (HMPV) and adenovirus (AdV), are major pathogens in lower respiratory infection other than bacteria. According to previous studies, nearly 40% of inpatients hospitalized with respiratory virus infection would develop sepsis after viral infection [1,2]. During sepsis, the cytokine storm seriously impacts the clinical prognoses by inducing immune dysfunction and multiorgan damages [3–5]. Thus, earlier clearance of the virus is crucial, which relies on the key role of lymphocyte, especially human natural killer (NK) cells and T cells in the immune system [6].

However, under many circumstances, massive apoptosis and exhaustion of lymphocytes would be induced by virus and cytokine storm, particularly in severe cases [7–10], resulting in lymphopenia. Lymphopenia has been identified strongly associated with disease severity and poor outcomes of virus infection, e.g., sepsis, multi-organ dysfunction syndrome, and death [11–14]. A previous meta-analysis also reported a 3-4-fold high risk of developing severe Coronavirus Disease 2019 (COVID-19) or death after lymphopenia occurred [15].

Nevertheless, lymphocyte count keeps changing with the disease progression and the change would be more rapid in severe conditions. Using single observation of peripheral lymphocyte count for afterwards prognoses estimation, which have been applied by most previous studies, would increase the risk of bias, as more information was hidden in the whole hospitalization [16]. However, no studies elucidated the impact of prolonged lymphopenia on worse outcome in the way of quantitative risk among inpatients with SARS-CoV-2 and influenza virus infection. Data were even less reported in other respiratory virus infections.

Therefore, in this study, we aimed to detailly describe the dynamic change of lymphocytes and estimate the quantitative risk of prolonged lymphopenia for disease progression and clinical prognoses, by extracting the time-series data of patients with SARS-CoV-2, influenza virus and other respiratory virus infections under routine clinical practice during hospitalization, thus provide more precise and relevant information to clinical practice.

2. Methods

2.1. Study design and patients

This was a retrospective cohort study among adult inpatients admitted into China-Japan Friendship Hospital between January 1st, 2016, and February 1st, 2023. Patients with laboratory-confirmed respiratory virus infection within 48 h after admission were involved. Pregnant women were excluded. Patient's information was acquired from the electronic medical records system (EMR), including clinical features, all measures of laboratory findings, prescriptions, and medical operations, etc. As only sporadic COVID-19 cases were reported between April 2020 and December 2022 in China, only those who admitted to China-Japan Friendship Hospital during the pandemic of omicron strain in December 2022 to January 2023 were included in this study. Finally, a total of 2388 inpatients were involved in this study, including 1440 (60.3 %) males and 948 (39.7 %) females, and the median age was 66 years old.

2.2. Patient consent statement

Ethical approval was obtained from China-Japan Friendship Hospital Ethics Committee (approval number: 2023-KY-078-1). As an observational study based on retrospective data, written informed consent forms (ICF) were exempted and only routine clinical microbiology and laboratory tests and respiratory samples collection were permitted.

2.3. Virological detection

Respiratory specimens (including nasopharyngeal swab, sputum, bronchoalveolar lavage fluid, and endotracheal aspirate) were collected for the detection of influenza virus, SARS-CoV-2, and other respiratory viruses (RSV, PIV, human rhinovirus, coronavirus, HMPV and AdV). Viruses were detected by real-time PCR (TaqMan Array Microfluidic Cards; Applied Biosystems, Foster City, CA, USA).Quick tests by antigens were also applied for influenza virus (Clearview Exact Influenza A&B; Alere, Waltham, MA, USA).

2.4. Outcomes and definitions

The primary outcome was in-hospital all-cause death. The secondary outcomes included multi-organ damages, lymphopenia,

Table 1
Demographic and clinical characteristics of patients on admission.

Characteristics	Influenza			SARS-CoV-2			Other respiratory viruses		
	Survival N = 385	Death N = 51	p	Survival N = 1286	Death N = 211	p	Survival N = 291	Death N = 28	p
Demographic and clinical characteristics									
Age, years	61.0 (49.0–72.0)	63.0 (49.0–72.0)	0.7647	67.0 (54.0–79.0)	80.0 (68.0–88.0)	<0.0001	62.0 (48.0–72.0)	69.0 (55.5–79.0)	0.0512
>65	136 (35.3)	21 (41.2)	0.4133	691 (53.7)	163 (77.3)	<0.0001	118 (40.5)	18 (64.3)	0.0153
Male	217 (56.4)	36 (70.6)	0.0531	760 (59.1)	144 (68.2)	0.0118	169 (58.1)	21 (75.0)	0.0814
Hypertension	150 (39.0)	20 (39.2)	0.9720	577 (44.9)	114 (54.0)	0.0134	107 (36.8)	11 (39.3)	0.7923
Chronic obstructive lung disease	57 (14.8)	5 (9.8)	0.3366	96 (7.5)	15 (7.1)	0.8549	43 (14.8)	5 (17.9)	0.6700
Malignancy	34 (8.8)	3 (5.9)	0.4572	210 (16.3)	19 (9.0)	0.0061	33 (11.3)	5 (17.9)	0.3358
Diabetes mellitus	110 (28.6)	8 (15.7)	0.0516	405 (31.5)	82 (38.9)	0.0342	68 (23.4)	6 (21.4)	0.8164
Chronic kidney disease	41/384 (10.7)	16/51 (31.4)	<0.0001	130/1250 (10.4)	41/198 (20.7)	<0.0001	26/289 (9.0)	10/28 (35.7)	0.0003
Chronic respiratory disease	151/384 (39.3)	15/51 (29.4)	0.1710	301/1250 (24.1)	58/198 (29.3)	0.1145	137/289 (47.4)	14/28 (50.0)	0.7929
Cardiovascular disease	92/384 (24.0)	17/51 (33.3)	0.1466	339/1250 (27.1)	124/198 (62.6)	<0.0001	87/289 (30.1)	16/28 (57.1)	0.0035
Hepatopathy	28/384 (7.3)	6/51 (11.8)	0.2906	49/1250 (3.9)	7/198 (3.5)	0.7942	11/289 (3.8)	1/28 (3.6)	0.9500
Laboratory findings									
PT, s	13.6 (13.0–14.4)	14.6 (13.6–16.0)	<0.0001	13.6 (13.1–14.4)	14.6 (13.8–16.1)	<0.0001	13.8 (13.2–14.7)	16.0 (14.9–21.0)	<0.0001
APTT, s	40.7 (35.7–47.1)	43.1 (38.3–51.4)	0.0421	38.1 (35.3–41.2)	50.0 (37.3–50.1)	0.1426	39.0 (35.3–45.0)	46.1 (41.0–56.5)	0.0003
Prolonged PT or APTT	160/360 (44.4)	31/50 (62.0)	0.0197	69/1135 (6.1)	55/204 (27.0)	<0.0001	97/274 (35.4)	19/25 (76.0)	<0.0001
BNP, pg/ml	78.0 (39.9–216.0)	142.8 (66.8–404.2)	0.0068	87.0 (39.0–205.0)	232.0 (111.5–569.0)	<0.0001	93.5 (36.6–281.6)	235.0 (95.2–700.5)	0.0390
NT-proBNP, pg/ml	300.0 (91.0–964.0)	992.0 (313.0–5766.0)	0.0004	368.5 (114.0–1031.5)	1298.5 (497.5–4938.5)	<0.0001	232.0 (90.0–925.0)	1786.0 (1071.0–8739.0)	<0.0001
Elevated BNP/NT-proBNP	180/306 (58.8)	42/48 (87.5)	0.0001	664/1047 (63.4)	192/203 (94.6)	<0.0001	147/254 (57.9)	21/24 (87.5)	0.0046
White blood cell count, $\times 10^9$/L	6.3 (4.4–9.0)	9.0 (4.4–11.3)	0.0064	5.9 (4.4–8.0)	8.3 (5.4–11.3)	<0.0001	7.2 (5.4–9.7)	10.2 (5.8–14.8)	0.0244
4-10	246/383 (64.2)	24/51 (47.1)	0.0087	855/1227 (69.7)	105/209 (50.2)	<0.0001	181/286 (63.3)	10/27 (37.0)	0.0090
<4	65/383 (17.0)	8/51 (15.7)		222/1227 (18.1)	25/209 (12.0)		38/286 (13.3)	3/27 (11.1)	
>10	72/383 (18.8)	19/51 (37.3)		150/1227 (12.2)	79/209 (37.8)		67/286 (23.4)	14/27 (51.9)	
Lymphocyte count, $\times 10^9$/L	1.1 (0.7–1.5)	0.5 (0.3–0.7)	<0.0001	0.9 (0.6–1.4)	0.5 (0.4–0.9)	<0.0001	1.2 (0.7–1.7)	0.6 (0.4–1.0)	<0.0001
Lymphocyte percentage	17.3 (10.2–26.7)	7.0 (3.6–10.3)	<0.0001	16.6 (9.7–26.4)	7.5 (3.8–12.5)	<0.0001	16.9 (10.1–26.1)	5.5 (4.2–10.7)	<0.0001
Lymphopenia on admission	*201/383 (52.5)*	*45/51 (88.2)*	*<0.0001*	*726/1225 (59.3)*	*179/209 (85.6)*	*<0.0001*	*133/286 (46.5)*	*21/27 (77.8)*	*0.0019*
Hemoglobin, g/L	126.0 (111.0–137.0)	127.0 (103.0–141.0)	0.6528	122.0 (109.0–136.0)	116.0 (95.0–132.0)	0.0006	122.0 (105.0–133.0)	106.0 (91.0–121.0)	0.0009
Anemia	116/383 (30.3)	21/51 (41.2)	0.1160	428/1227 (34.9)	97/209 (46.4)	0.0014	114/286 (39.9)	20/27 (74.1)	0.0006
Platelet count, $\times 10^9$/L	189.5 (138.5–241.0)	158.0 (118.0–199.0)	0.0056	188.0 (143.0–246.0)	157.0 (106.0–223.0)	<0.0001	214.0 (160.0–279.0)	132.5 (106.0–181.0)	<0.0001
50 - 100	39/372 (10.5)	6/49 (12.2)	0.9097	66/1226 (5.4)	35/209 (16.7)	<0.0001	12/273 (4.4)	2/26 (7.7)	0.0095
<50	6/372 (1.6)	1/49 (2.0)		16/1226 (1.3)	9/209 (4.3)		5/273 (1.8)	4/26 (15.4)	
≥100	327/372 (87.9)	42/49 (85.7)		1144/1226 (93.3)	165/209 (78.9)		256/273 (93.8)	20/26 (76.9)	
Alanine transaminase, U/L	24.0 (16.0–44.0)	34.0 (23.0–60.0)	0.0073	23.0 (14.0–38.0)	25.0 (16.0–38.0)	0.1306	22.0 (14.0–36.0)	28.0 (12.0–70.0)	0.4078
>40	108/373 (29.0)	22/50 (44.0)	0.0304	235/1048 (22.4)	43/199 (21.6)	0.7999	60/280 (21.4)	9/27 (33.3)	0.1570
Creatinine, μmol/L	67.5 (53.4–86.5)	78.2 (54.1–108.5)	0.0614	68.1 (53.7–89.7)	88.3 (64.6–130.4)	<0.0001	69.4 (55.7–86.0)	101.7 (53.9–152.1)	0.0090
>133	31/377 (8.2)	8/50 (16.0)	0.0967	136/1072 (12.7)	49/200 (24.5)	<0.0001	25/279 (9.0)	8/27 (29.6)	0.0043
Lactate dehydrogenase, U/L	229.0 (190.0–339.0)	472.0 (394.0–675.0)	<0.0001	229.5 (183.0–303.0)	389.0 (280.0–547.0)	<0.0001	227.0 (177.0–333.0)	358.0 (273.0–618.0)	<0.0001
>245	129/309 (41.7)	38/41 (92.7)	<0.0001	270/624 (43.3)	140/161 (87.0)	<0.0001	100/241 (41.5)	20/25 (80.0)	0.0002
Creatine kinase, U/L	72.0 (44.0–156.0)	93.0 (38.0–292.0)	0.3178	55.0 (32.0–92.0)	105.0 (49.0–243.0)	<0.0001	54.5 (33.5–98.0)	205.0 (56.5–848.0)	0.0013
Creatine kinase >185, U/L	63/306 (20.6)	12/39 (30.8)	0.1466	67/627 (10.7)	51/157 (32.5)	<0.0001	35/240 (14.6)	12/24 (50.0)	0.0001
D-dimer, μg/ml	1.0 (0.4–2.3)	3.2 (1.4–7.5)	<0.0001	0.8 (0.4–1.8)	2.3 (1.1–4.9)	<0.0001	0.8 (0.4–2.2)	3.4 (1.1–6.2)	0.0004
>0.5	79/347 (22.8)	5/43 (11.6)	0.0003	303/1097 (27.6)	33/188 (17.6)	<0.0001	65/271 (24.0)	4/21 (19.0)	0.0023

(*continued on next page*)

Table 1 (*continued*)

Characteristics	Influenza			SARS-CoV-2			Other respiratory viruses		
	Survival N = 385	Death N = 51	p	Survival N = 1286	Death N = 211	p	Survival N = 291	Death N = 28	p
>1	170/347 (49.0)	35/43 (81.4)		463/1097 (42.2)	148/188 (78.7)		115/271 (42.4)	16/21 (76.2)	
≤0.5	98/347 (28.2)	3/43 (7.0)		331/1097 (30.2)	7/188 (3.7)		91/271 (33.6)	1/21 (4.8)	
Serum Ferritin, μg/L	344.3 (137.9–669.3)	854.6 (551.6–2292.0)	0.0028	366.6 (184.0–664.2)	655.8 (334.9–1242.2)	<0.0001	225.6 (120.6–642.0)	882.6 (685.7–1832.0)	0.1308
>300	40/69 (58.0)	16/19 (84.2)	0.0353	253/449 (56.3)	79/97 (81.4)	<0.0001	34/76 (44.7)	4/5 (80.0)	0.1166
Procalcitonin, ng/ml	0.3 (0.2–0.8)	0.9 (0.4–5.3)	<0.0001	0.2 (0.1–0.7)	0.6 (0.3–2.1)	<0.0001	0.3 (0.2–0.6)	0.8 (0.5–4.8)	<0.0001
0.1–0.24	78/266 (29.3)	8/47 (17.0)	<0.0001	154/330 (46.7)	26/123 (21.1)	<0.0001	79/176 (44.9)	2/26 (7.7)	<0.0001
0.25–0.4	82/266 (30.8)	4/47 (8.5)		52/330 (15.8)	27/123 (22.0)		48/176 (27.3)	6/26 (23.1)	
<0.1	11/266 (4.1)	1/47 (2.1)		18/330 (5.5)	3/123 (2.4)		3/176 (1.7)	0/26 (0.0)	
≥0.5	95/266 (35.7)	34/47 (72.3)		106/330 (32.1)	67/123 (54.5)		46/176 (26.1)	18/26 (69.2)	
Neutrophil count, $\times 10^9$/L	4.4 (2.9–7.1)	8.0 (4.0–10.4)	<0.0001	4.2 (2.9–6.3)	6.9 (4.5–10.4)	<0.0001	5.1 (3.4–7.4)	8.9 (5.1–13.8)	0.0007
1.8–6.3	235/383 (61.4)	14/51 (27.5)	<0.0001	837/1225 (68.3)	81/209 (38.8)	<0.0001	168/286 (58.7)	8/27 (29.6)	0.0120
<1.8	31/383 (8.1)	3/51 (5.9)		87/1225 (7.1)	12/209 (5.7)		18/286 (6.3)	2/27 (7.4)	
>6.3	117/383 (30.5)	34/51 (66.7)		301/1225 (24.6)	116/209 (55.5)		100/286 (35.0)	17/27 (63.0)	
eGFR, ml/min/1.73 m^2/L	95.2 (74.9–107.7)	84.4 (58.7–104.8)	0.0494	88.2 (67.8–100.5)	67.6 (44.0–89.4)	<0.0001	94.2 (78.1–106.2)	60.4 (44.8–97.4)	0.0004
60-90	102/368 (27.7)	15/50 (30.0)	0.1035	355/1031 (34.4)	69/192 (35.9)	<0.0001	64/239 (26.8)	5/23 (21.7)	0.0004
<60	56/368 (15.2)	13/50 (26.0)		205/1031 (19.9)	77/192 (40.1)		30/239 (12.6)	11/23 (47.8)	
≥90	210/368 (57.1)	22/50 (44.0)		471/1031 (45.7)	46/192 (24.0)		145/239 (60.7)	7/23 (30.4)	
Corticosteroids	102 (26.5)	31 (60.8)	<0.0001	432 (33.6)	93 (44.1)	0.0031	104 (35.7)	19 (67.9)	0.0009
Days from admission to corticosteroids treatment	2.0 (1.0–4.0)	2.0 (1.0–6.0)	0.2808	1.0 (1.0–2.0)	2.0 (1.0–4.0)	0.0006	1.0 (1.0–4.0)	2.0 (1.0–5.0)	0.3934

Notes. Data were expressed as number (%) or median (interquartile range). P values were estimated by Chi-square test, Fisher's exact test or Kruskal-Wallis test, where appropriate. Other respiratory viruses included respiratory syncytial virus, parainfluenza virus, human rhinovirus, coronavirus, human metapneumovirus and adenovirus. Abbreviations: WBC, white blood cell; PT, thromboplastin time; APTT, activated partial thromboplastin time; BNP, brain natriuretic peptide; NT-proBNP, N-terminal pro-brain natriuretic peptide; LDH, lactate dehydrogenase; eGFR, estimated glomerular filtration rate.

suspected secondary bacterial infection, intensive care unit (ICU) admission, noninvasive mechanical ventilation (NIMV), invasive mechanical ventilation (IMV), extracorporeal membrane oxygenation (ECMO), vasoactive drug administration and length of hospital stay.

Acute kidney injury (AKI) was defined according to the "Kidney Disease: Improving Global Outcomes" (KDIGO) guidelines [17]. Renal insufficiency was defined as an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2, assessed by CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula [18]. Liver injury was recognized when at least one of the following abnormal liver function tests were found: aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 times the upper reference limit (URL), bilirubin above the URL, albumin <35 g/L [19]. Myocardial injury was defined as hypersensitive troponin I (HsTNI) ≥ 0.0198 ng/ml or troponin T (TNT) ≥ 0.014 ng/ml [20]. Hyperckemia was defined as creatine kinase >1000 U/L. Elevated brain natriuretic peptide (BNP)/N-terminal pro-brain natriuretic peptide (NT-proBNP) was defined as BNP ≥100 pg/ml or NT-proBNP ≥125 pg/ml. Suspected secondary bacterial infection was defined as procalcitonin (PCT) ≥ 0.5 ng/ml during hospitalization. Lymphopenia was defined as the absolute lymphocyte count <1.1 × 10^9/L. Low platelet was defined as platelet count <50 × 10^9/L.

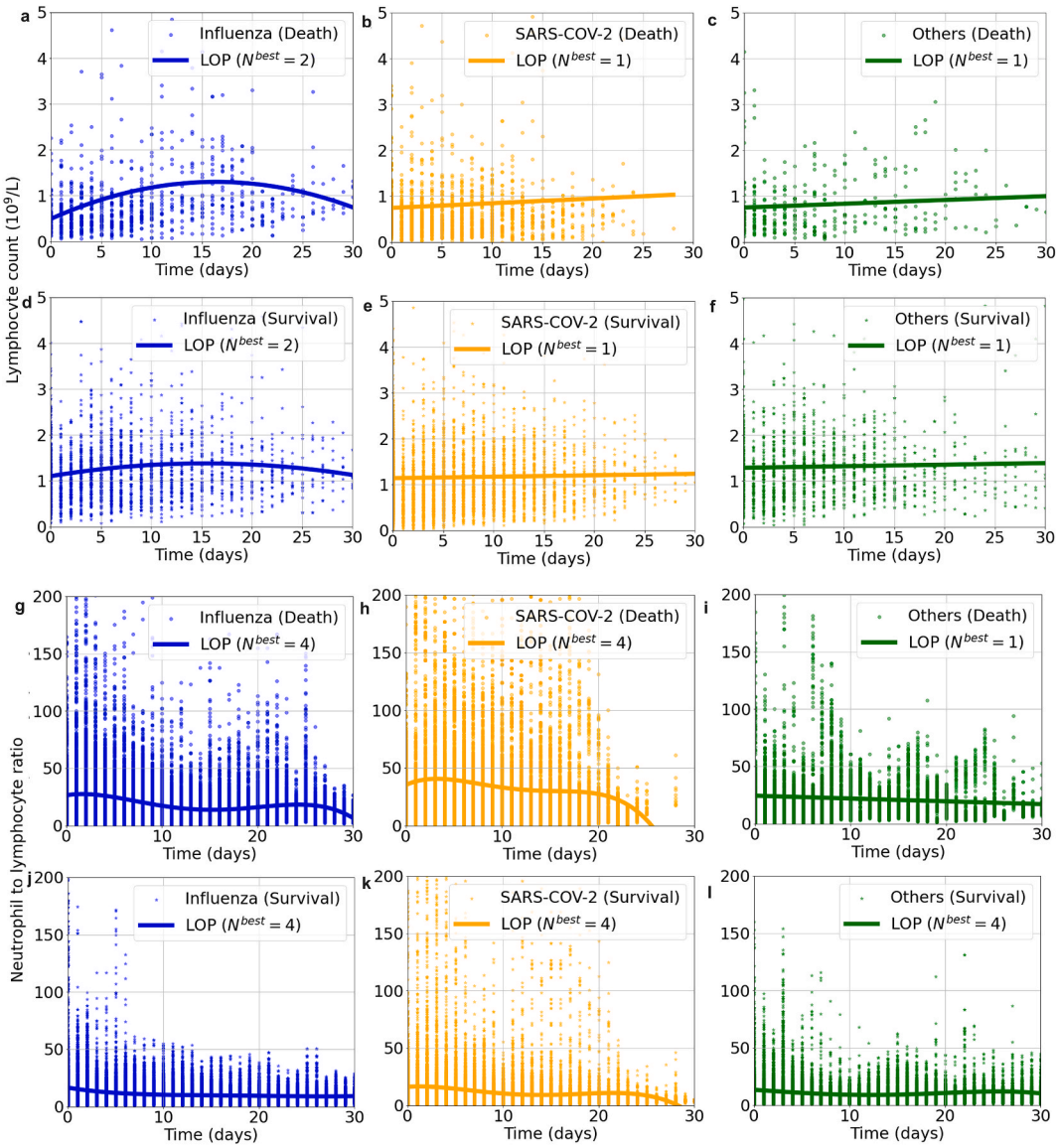

Fig. 1. The dynamic changes of lymphocyte count [panel a–f] and neutrophil to lymphocyte ratio [panel g–l] in patients hospitalized with respiratory virus infections by Legendre orthogonal polynomials.
Note: N^{best} refers to the appropriate order of fit for LOP by the Bayesian information criterion method. Other respiratory viruses included respiratory syncytial virus, parainfluenza virus, human rhinovirus, coronavirus, human metapneumovirus and adenovirus.
Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; LOP, Legendre orthogonal polynomials.

Table 2
Clinical prognoses of patients hospitalized with respiratory virus infection.

Characteristics	Influenza			SARS-CoV-2			Other respiratory viruses		
	Survival N = 385	Death N = 51	p	Survival N = 1286	Death N = 211	p	Survival N = 291	Death N = 28	p
Lymphopenia during hospitalization	240/383 (62.7)	51/51 (100.0)	<0.0001	867/1227 (70.7)	198/209 (94.7)	<0.0001	158/286 (55.2)	25/27 (92.6)	0.0002
Lasting for 1–2 days	111/383 (29.0)	4/51 (7.8)	<0.0001	338/1226 (27.6)	39/207 (18.8)	<0.0001	70/286 (24.5)	7/27 (25.9)	0.0002
Lasting for 3–7 days	77/383 (20.1)	20/51 (39.2)		234/1226 (19.1)	68/207 (32.9)		45/286 (15.7)	9/27 (33.3)	
Lasting for more than 7 days	52/383 (13.6)	27/51 (52.9)		294/1226 (24.0)	89/207 (43.0)		43/286 (15.0)	9/27 (33.3)	
Longest duration of lymphopenia	1.0 (0.0, 4.0)	8.0 (5.0, 12.0)	<0.0001	1.0 (0.0, 7.0)	7.0 (3.0, 10.0)	<0.0001	1.0 (0.0, 5.0)	6.0 (2.0, 9.0)	<0.0001
Acute kidney injury	68/377 (18.0)	32/50 (64.0)	<0.0001	112/1074 (10.4)	95/201 (47.3)	<0.0001	47/279 (16.8)	16/27 (59.3)	<0.0001
Liver injury	80/373 (21.4)	38/50 (76.0)	<0.0001	154/1049 (14.7)	89/199 (44.7)	<0.0001	58/280 (20.7)	20/27 (74.1)	<0.0001
Hyperckemia	17/306 (5.6)	3/39 (7.7)	0.6053	9/627 (1.4)	14/157 (8.9)	<0.0001	9/240 (3.8)	7/24 (29.2)	0.0001
Myocardial injury	142/238 (59.7)	28/30 (93.3)	0.0003	524/1058 (49.5)	200/205 (97.6)	<0.0001	102/227 (44.9)	23/23 (100.0)	<0.0001
Elavated BNP/ NTproBNP	186/306 (60.8)	46/48 (95.8)	<0.0001	732/1049 (69.8)	204/206 (99.0)	<0.0001	161/255 (63.1)	24/24 (100.0)	0.0003
Low platelet	16/373 (4.3)	24/50 (48.0)	<0.0001	35/1226 (2.9)	44/209 (21.1)	<0.0001	12/273 (4.4)	11/26 (42.3)	<0.0001
Suspected secondary bacterial infection	111/269 (41.3)	47/49 (95.9)	<0.0001	160/354 (45.2)	121/145 (83.4)	<0.0001	63/183 (34.4)	26/27 (96.3)	<0.0001
Oxygen support	20 (5.2)	11 (21.6)	0.0003	122 (9.5)	15 (7.1)	0.2669	26 (8.9)	2 (7.1)	0.7422
NIMV	69 (17.9)	20 (39.2)	0.0004	26 (2.0)	21 (10.0)	<0.0001	22 (7.6)	3 (10.7)	0.5706
IMV	57 (14.8)	45 (88.2)	<0.0001	22 (1.7)	67 (31.8)	<0.0001	20 (6.9)	20 (71.4)	<0.0001
ECMO	10 (2.6)	17 (33.3)	<0.0001	2 (0.2)	8 (3.8)	<0.0001	3 (1.0)	5 (17.9)	0.0001
vasoactive drug	106 (27.5)	36 (70.6)	<0.0001	76 (5.9)	108 (51.2)	<0.0001	81 (27.8)	25 (89.3)	<0.0001
ICU admission	95 (24.7)	47 (92.2)	<0.0001	64 (5.0)	72 (34.1)	<0.0001	45 (15.5)	21 (75.0)	<0.0001
Length of stay	11.0 (8.0–16.0)	12.0 (8.0–22.0)	0.2948	12.0 (8.0–16.0)	10.0 (6.0–14.0)	0.0002	11.0 (8.0–15.0)	8.5 (5.5–17.5)	0.1350
At least one secondary outcome	335 (87.0)	51 (100.0)	0.0062	1060 (82.4)	209 (99.1)	<0.0001	231 (79.4)	27 (96.4)	0.0285
Without any secondary outcome	50 (13.0)	0 (0.0)	0.0062	226 (17.6)	2 (0.9)	<0.0001	60 (20.6)	1 (3.6)	0.0285

Notes. Data were expressed as number (%) or median (interquartile range). P values were estimated by Chi-square test, Fisher's exact test or Kruskal-Wallis test, where appropriate. Other respiratory viruses included respiratory syncytial virus, parainfluenza virus, human rhinovirus, coronavirus, human metapneumovirus and adenovirus. Secondary outcomes referred to lymphopenia during hospitalization, acute kidney injury, liver injury, hyperckemia, myocardial injury, elevated BNP/NTproBNP, low platelet, suspected secondary bacterial infection, NIMV, IMV, ECMO, vasoactive drug and ICU admission.
Abbreviations: BNP, brain natriuretic peptide; NT-pro BNP, N-terminal pro-brain natriuretic peptide; NIMV, noninvasive mechanical ventilation; IMV, invasive mechanical ventilation; ECMO, extracorporeal membrane oxygenation.

2.5. Statistical analysis

Baseline patients' characteristics were expressed in terms of descriptive statistics. Categorical variables were summarized as frequency (percentage). Continuous variables were presented as median (interquartile range, IQR). P values were calculated by Mann-Whitney U test, χ^2 test or Fisher exact test where appropriate. The data imputation was not performed in this study. All tests were two-sided and were considered statistically significant at a p-value of <0.05.

We divided respiratory virus infections into three categories according to previous experiences and study: influenza virus, SARS-CoV-2, and other respiratory viruses [2]. Considering the absolute values of lymphocytes to track changes over time does not adequately capture its impact on clinical outcomes and may lead to unexpecting bias, the duration of days below the lower threshold can offer insights into the progression of the immune dysregulation. Therefore, in this study, we introduced a statistical metric to describe the absolute counts change of peripheral lymphocyte: the duration below the lower bound, $D(i)$.

$$D(i) = \begin{cases} t - t_{\text{previous}} & \text{if } \chi(R_i(t)) \times \chi\left(R_i\left(t_{\text{previous}}\right)\right) = 1 \\ 1 & \text{otherwise} \end{cases}$$

Where, $R_i(t)$ represented the index for the i patient at time t. $\Delta R_i(t) = R_i(t) - R_i(t-1)$ denoted the change at time t. Δt was typically one day but could be shorter or longer, depending on the frequency of laboratory test. The duration of lymphopenia was then divided into lasting for 1–2 days, 3–7 days and >7 days.

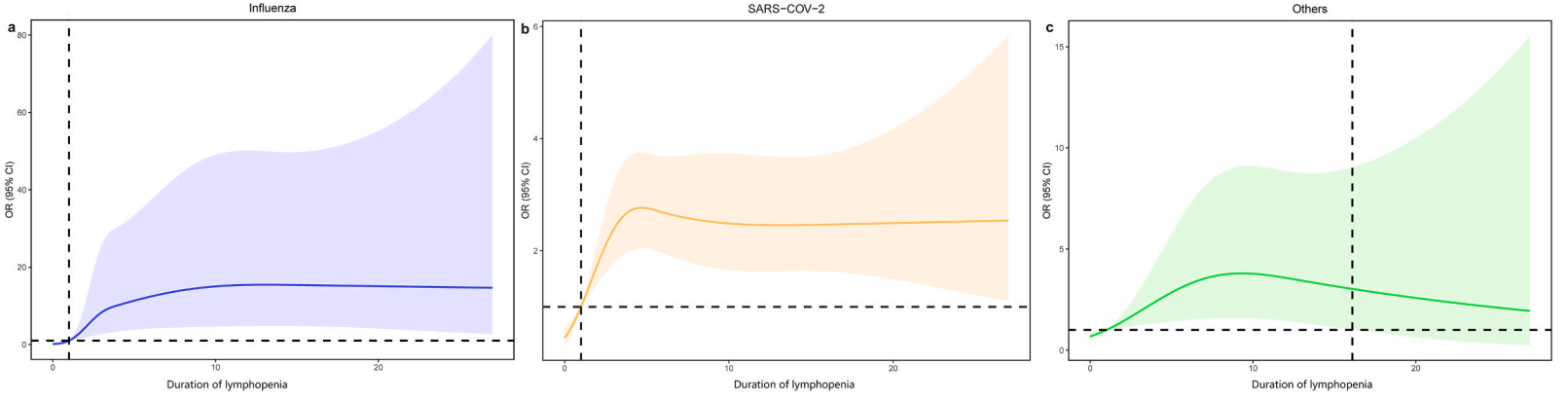

Fig. 2. Associations of prolonged lymphopenia with death in patients hospitalized with influenza [panel a], SARS-CoV-2 [panel b] and other respiratory virus infections [panel c].
Notes: The OR curves were portrayed by restricted cubic splines. Other respiratory viruses included respiratory syncytial virus, parainfluenza virus, human rhinovirus, coronavirus, human metapneumovirus and adenovirus.
Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; OR, odds ratio; 95 % CI, 95 % confidence interval.

Table 3
Multivariable analysis of the association between prolonged lymphopenia and death outcome.

Risk factors	Influenza		SARS-CoV-2		Other respiratory viruses	
	OR (95 % CI)	p	OR (95 % CI)	p	OR (95 % CI)	p
Duration of lymphopenia						
1–2 days	Reference		Reference		Reference	
3–7 days	7.20 (2.27–22.77)	0.0008	3.07 (1.89–5.01)	<0.0001	1.61 (0.46–5.66)	0.4538
More than 7 days	17.80 (5.21–60.82)	<0.0001	6.28 (3.53–11.18)	<0.0001	3.23 (0.79–13.21)	0.1031
Length of stay	0.96 (0.93–1.01)	0.0862	0.85 (0.81–0.89)	<0.0001	0.92 (0.85–1.00)	0.0417
Age >65 years	1.05 (0.50–2.22)	0.8988	2.06 (1.34–3.17)	0.0009	2.52 (0.92–6.94)	0.0737
Corticosteroids	2.08 (1.04–4.15)	0.0371	1.33 (0.91–1.93)	0.1360	3.07 (1.05–8.99)	0.0406
Chronic kidney disease	2.37 (1.04–5.38)	0.0395	1.52 (0.96–2.43)	0.0768	6.04 (1.92–19.01)	0.0021
Chronic respiratory disease	0.83 (0.37–1.85)	0.6526	1.33 (0.90–1.98)	0.1512	1.01 (0.38–2.71)	0.9782
Cardiovascular disease	0.84 (0.40–1.77)	0.6397	3.19 (2.21–4.60)	<0.0001	1.45 (0.52–3.99)	0.4765
Lymphopenia on admission	0.78 (0.27–2.25)	0.6392	0.88 (0.46–1.67)	0.6909	0.54 (0.13–2.20)	0.3926

Notes. P values, odds ratios and 95 % confidence intervals were estimated by Logistic regression. Other respiratory viruses included respiratory syncytial virus, parainfluenza virus, human rhinovirus, coronavirus, human metapneumovirus and adenovirus.
Abbreviations: OR, odds ratio; CI, confidence interval.

2.5.1. Legendre orthogonal polynomials

In this study, we applied Legendre orthogonal polynomials (LOP) to capture the serial trends of different markers to minimize the information bias in data collection due to missing data. Legendre polynomials were a classical series of orthogonal polynomials widely used in mathematics and physics. They could be employed to approximate any function, particularly those defined on the interval [−1, 1]. The approximation of a function using Legendre polynomials was a numerical method that involves expressing the function as a linear combination of these orthogonal polynomials. The Legendre polynomial basis was defined as follows,

$$P_0(x) = 1, P_1(x) = x, P_{n+1}(x) = \frac{(2n+1)xP_n(x) - nP_{n-1}(x)}{n+1}$$

Where, n represents degrees of Legendre polynomials.

Compared to a polynomial basis, Legendre polynomials had orthogonality over the interval [−1, 1], i.e.

$$\int_{-1}^{1} P_m(x)P_k(x)dx = 0.\ m \neq k$$

Since the orthogonal property of this basis made it the most excellent basis, higher orders did not affect the contribution of lower orders, which could not be avoided for polynomial bases $\{1, x, x^2, x^3 \cdots\}$. To determine the appropriate order of fit for LOP, we utilized the Bayesian information criterion (BIC) method.

$$\mathrm{BIC} = -2 \cdot \ln(\mathrm{L}) + \mathrm{k} \cdot \ln(\mathrm{n})$$

Where, L represented the maximum likelihood estimate for LOP, n denoted the number of samples, and k signified the count of parameters.

2.5.2. Restricted cubic splines (RCS)

RCS were methods for analyzing the nonlinear relationships between features and outcomes. This approach employed polynomials to fit data across specified intervals, ensuring smoothness at the intersecting knots. Restricted cubic spline functions were typically expressed as follows,

$$RCS(x, n) = \sum_{i=1}^{n-1} \beta_i S_i(x),$$

Where, Spline basis functions were $S_i(x) = (x - t_{i-1})_+^3 - \frac{(x-t_{n-1})_+^3 (t_n - t_{i-1})}{t_n - t_{n-1}} + \frac{(x-t_n)_+^3 (t_{n-1} - t_{i-1})}{t_n - t_{n-1}}, i = 1, 2, \cdots, n-1.$ $(x - t_i)_+^3$ meant that if $x \geq \mathrm{t_j}$, then took $(x - t_i)^3$; otherwise, took 0.

Moreover, to quantitively estimate the risk of prolonged lymphopenia during hospitalization, multivariable logistic regressions (adjusted for age, corticosteroids, chronic kidney disease, chronic respiratory disease, cardiovascular disease, length of hospital stay and lymphopenia on admission) were performed. Analyses were performed using SAS 9.4 software (Cary, NC, USA) or python 3.7 (package "sklearn" and "mlxtend"), where appropriate.

3. Results

3.1. Demographic and clinical characteristics on admission

As is shown in Table 1, patients died of COVID-19 or other respiratory virus infections were significantly older, comorbided with cardiovascular disease or CKD than those survived ($P < 0.05$). Most of the deaths were males or with CKD in influenza infection and COVID-19. The rate of diabetes mellitus was higher in death group of COVID-19, while for patients with influenza infection, the higher rate was in survival group. (Table 1).

Patients died had more significant abnormalities than those survived in common laboratory markers for influenza, SARS-CoV-2 and other respiratory virus infections, manifesting as: higher prolonged thromboplastin time (PT) or activated partial thromboplastin time (APTT) rate, elevated BNP/NT-proBNP rate, white blood cell (WBC) count, lymphopenia rate, anemia, low platelet rate, lactate dehydrogenase (LDH), creatine kinase (CK), d-dimer, serum ferritin (SF), PCT, neutrophil count, low eGFR rate and high corticosteroids administration rate. Specially, patients died with influenza infection were observed higher rates of ALT >40 U/L, while for SARS-CoV-2 or other respiratory virus infections, more serum creatinine (Scr) > 133 μmol/L cases were found at admission. (Table 1).

3.2. Dynamic changes of laboratory results

According to Fig. 1, Supplementary Fig. 1, Supplementary Fig. 2, and Supplementary Fig. 3, similar dynamic immune changes among different virus infection were noted during hospitalization: lymphocyte counts were generally lower in dead cases than the survivals and a trend of elevation was observed only in survival groups. In patients with influenza infection, the lymphocyte counts transiently increased from the baseline on admission, but then constantly declined as days of hospital stay prolonged, especially in those dead cases. Neutrophil to lymphocyte ratio (NLR) increased in death group of COVID-19, while maintained low and steady and gradually decreased in other subgroups. WBC counts also surged then slowly decreased during hospitalization in death groups, while changed relatively gently in survival groups (Fig. 1, Supplementary Fig. 1). While for those administered with corticosteroids, the lymphocyte counts were slightly lower during hospitalization. (Supplementary Fig. 2).

As for other biomarkers, the PCT, C-reactive protein (CRP), Scr and SF levels were higher in death groups than in the survival groups for all respiratory virus infections. Of note, patients infected with SARS-CoV-2 had generally numerically lower PCT level during hospitalization in both death and survival groups than those infected with other viruses. (Supplementary Fig. 3).

3.3. Clinical prognoses

As shown in Table 2, the death rate in SARS-CoV-2 was 14.0 % (211/1497), followed by 11.7 % (51/436) in influenza and 8.8 % (28/319) in other respiratory virus infections. During hospitalization, longest duration of lymphopenia, lymphopenia, the rates of longest duration of lymphopenia, AKI, liver injury, myocardial injury, elevated BNP/NT-proBNP, low platelet, suspected secondary bacterial infection, machinal ventilation, ECMO, vasoactive drug and ICU admission were all higher, and the length of hospital stay was all longer in death groups for all viruses. Of note, the longest duration of lymphopenia was 8 days (IQR 5.0–12.0) in death group of influenza, numerically longer than that of SARS-CoV-2 and other respiratory virus infections. Hyperckemia was found significantly higher in only death groups of SARS-CoV-2 and other respiratory virus infections. For influenza virus, 335 (87.0 %) patients were with at least one secondary outcome and 50 (13.0 %) were without any secondary outcome among survivors; for SARS-CoV-2, the cases (proportions) were 1060 (82.4 %) and 226 (17.6 %), respectively; for other respiratory viruses, they were 231 (79.4 %) and 60 (20.6 %). (Table 2).

The RCS and inflection points of duration of lymphopenia were shown in Fig. 2. Prolonged lymphopenia rapidly increased death risk in the first several days for all respiratory infection and gradually turned into high but stable level. (Fig. 2).

The logistic regressions in Table 3 and Supplementary Table 1 showed that prolonged lymphopenia was significantly associated with death in influenza and SARS-CoV-2, but not in other respiratory viruses. The associations were stronger in influenza as the lymphopenia prolonged in influenza virus infection than that in SARS-CoV-2 infection. After the adjustment for age, corticosteroids, chronic kidney disease, chronic respiratory disease, cardiovascular disease, lymphopenia on admission and length of hospital stay, the duration of lymphopenia was significantly associated with death in influenza (OR 7.20, 95 % CI 2.27–22.77, $p = 0.0008$ for lasting for 3–7 days; OR 17.80, 95 % CI 5.21–60.82, $p < 0.0001$ for lasting for more than 7 days) and SARS-CoV-2 (OR 3.07, 95 % CI 1.89–5.01, $p < 0.0001$ for lasting for 3–7 days; OR 6.28, 95 % CI 3.53–11.18, $p < 0.0001$ for lasting for more than 7 days), compared with a transient lymphopenia of 1–2 days, while no association was found in other respiratory virus infections (Table 3).

For other clinical prognoses, analyses in Supplementary Fig. 4 showed that prolonged lymphopenia also associated with similar worse prognoses, e.g. AKI, ICU admission, invasive mechanical ventilation, liver injury and myocardial injury. While for other respiratory virus infections, prolonged lymphopenia was only associated with AKI. (Supplementary Fig. 4).

4. Discussion

In this retrospective cohort study, we described the dynamic change of lymphocyte count and its associations with clinical prognoses among patients hospitalized with influenza, SARS-CoV-2, and other respiratory virus infections. We innovatively quantified the increased risk of prolonged lymphopenia on prognoses in these patients, especially for those with influenza or SARS-CoV-2 infection. Compared with the previous study on the comparison of clinical features and outcomes among different respiratory

viruses [21], our study provided the most comprehensive description on lab markers and multi-organ damages for patients hospitalized with common respiratory virus infections.

Lymphopenia had been found associated with disease severity and poor outcomes in patients infected by respiratory viruses [14,22]. It was demonstrated that lymphopenia was a prominent feature of COVID-19 and influenza infections. Lymphocyte counts in peripheral blood maybe a useful and readily available biomarker for differential diagnosis [23], predicting severity and clinical outcome.However, sample sizes in previous studies were small and the mechanisms were different between SARS-CoV-2 and influenza [13,15,24,25]. For SARS-CoV-2, it had a broad tropism of major immune cells, including neutrophils, B cells, T cells and NK cells [26], and may directly infect $CD4^+$ T cell and induce apoptosis in the hypoxia-inducible factor-1a (HIF-1a)-dependent pathway [8]. Afterwards, strong inflammation would also be triggered by dying $CD4^+$ T cell and furtherly impact the adaptive immune system [8]. While during influenza infection, the virus directly infects NK cells and induces cell apoptosis [27]. As observed in mice during influenza infection, a transient increase of NK cytotoxicity is followed by a marked decrease in NK cell activity, with a virus dose-dependent effect [27]. However, during infections with very high load of influenza virus, increased NK cells facilitated its act in reducing T cell immunity, resulting in viral persistence and T cell exhaustion [28].

Prolonged lymphopenia and its quantitative effect on clinical prognoses have never been analyzed. Our innovative finding that prolonged lymphopenia had increased risk for death in influenza infection and relatively lower risk in SARS-CoV-2 infection was of higher clinical significance. Clinically, lymphopenia caused by corticosteroids was transient after a single administration of corticosteroids but could be sustained with the chronic elevation of plasma corticosteroids [10]. The effect of corticosteroids treatment on lymphocytes count was also considered in our study and did not show strong impact on the duration of lymphopenia, which might need more studies to verify. Nevertheless, our study indicated the impact of infection on lymphopenia may be stronger in influenza infection than that in COVID-19, as we found longer median duration of lymphopenia and higher magnitude in OR values. However, the underlying mechanisms remain to be revealed. Moreover, we found that for other respiratory virus infections, the occurrence of lymphopenia was important for worse prognoses prediction, rather than how long the lymphopenia would be lasting.

A high NLR implies an aberrant immune response and has been studied as a marker of poor prognosis for respiratory infections [29–31]. It was reported that NLR was lower at admission and has more prognostic value in COVID-19 patients compared with influenza and RSV, and had the potential for distinguishing COVID-19 from influenza infection [29,30]. In our study, the NLR of dead cases of COVID-19 kept highest compared with other virus infections during hospitalization, which may be resulted from the excessive neutrophil generation and activation [4] and the massive decline of lymphocyte in severe or critical COVID-19. The predictive value of NLR was verified in our study with the pandemic omicron strain, consistent with previous strains in 2020 [32–34]. However, like lymphopenia, no studies discussed the impact of higher NLR on prognoses from a dynamic perspective during hospitalization, which implies that more further studies are needed.

Besides all-cause death during hospitalization, the association between prolonged lymphopenia and major organ damage were demonstrated in our study as well. Prolonged lymphopenia, especially lasting for longer days, had stronger association with kidney, liver and cardiac injury, and higher level of respiratory support. This indicated that lymphopenia might be involved in more important roles during the progression after influenza or SARS-CoV-2 infection, and more research are warranted to verify these findings.

Complete blood count is one of the commonest tests in clinical practice, always with several repetition during hospitalization thus it would be instant and economic if more information could be obtained from it [31]. The investigation of clinical big data increases rapidly in recent years, and was one of the aims in our study. In this paper, we employed the LOP method which can be utilized to interpret complex, dispersed medical data. Our study exhibited a successful attempt in the application of mathematical methods on temporal and large amounts of clinical data. Another advantage of this study was that we compared the dynamic changes and impact of lymphopenia among the commonest respiratory viruses. It has been reported that the severity and outcomes of influenza and COVID-19 patients, but lymphopenia was not able to provide distinguishable information for those two kinds of virus [21]. We found the risk magnitude of lymphopenia differed between different virus infections. That might be used as a distinguished way to identify different viruses.

Some limitations must be claimed in this study. Firstly, in this single-center, retrospective study, selection bias was inevitable. Most patients involved in our study were severe to critical, with high rates of organ damage and death, especially in those hospitalized with influenza infection. Therefore, the comparisons between different virus infections were inappropriate. Secondly, the laboratory tests were performed following clinical necessity, and the missing values were difficult to traceback, so our analyses could only depend on the current available data. For other respiratory virus infections, more laboratory findings were absent than influenza and SARS-CoV-2, which led to potential imbalance in model fitting. However, the application of LOP method helped to describe temporal trends during hospitalization and were accurately portrayed as a curve with optimal fit of goodness, despite the nature of medical series data was discrete in distribution and the random missing. Thirdly, the subtypes of influenza were not recorded accurately in the retrospective database, which limited further investigation on the difference on different subtypes. Fourthly, among the subtypes of SARS-CoV-2, only the data of omicron variant were available in our study, so the difference between different SARS-CoV-2 variants were unavailable, and we could only compare our findings with previous literatures, regardless the kind of variant. Fifthly, duration of lymphopenia was valuable, but could only predict events occurring within or after the specified duration range category. For patients died before specific days of persistent lymphopenia, they would be excluded from specific analysis and the sample size would be smaller. Finally, although bacterial infection might be indicated by PCT, it was hard to be confirmed without the result of culture. Thus, we only described the condition as “suspected bacterial infection”. According to previous study, bacteria co-infections were common in both influenza and SARS-CoV-2 infections [35,36]. In our study, we observed that almost all dead cases in influenza were comorbid suspected secondary bacterial infection, while those with SARS-CoV-2 were not. The reason may lie in the acute alter in patients’ systemic Toll-like receptor (TLR) responses during the infection of influenza virus [36]. Nevertheless, more studies are necessary to

investigate the bacterial or even viral cross infection after hospitalization with respiratory virus infection.

For further clinical perspective, studies are required to mechanically prove the clinical manifestations revealed by our study. Beyond those, the method conducted in our study is also promising for adjuvant clinical decision, such as optimizing the opportunity of corticosteroids and other immune regulatory medications. For example, a clinical trial by Cheng et al. reported that recombinant human granulocyte colony-stimulating factor (rhG-CSF) may have the potential to reduce deterioration or death COVID-19 patients with lymphopenia [37]. Our study may provide a clue for the selections of treatment timing and specific patients to acquire better effect.

In summary, we found prolonged lymphopenia was significantly associated with worse clinical prognoses in influenza and SARS-CoV-2 infections, compared with a transient lymphopenia of 1-2 days, but not in other respiratory virus infections. The dynamic immune status changes and organ damages after infection were different between viruses.

Data availability statement

Data will be made available on request: readers can access the data by contacting the corresponding authors to acquire permission.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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