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T-cell lymphocytopenia: An omnipresent predictor of morbidity and mortality in consequence of SARS-CoV disease and influenza A infections

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ABSTRACT

Purpose of the research: We proposed *T*-cell lymphocytopenia as a strategic predictor of serious coronavirus and influenza infections. Our preeminent goal was to determine whether a degree of *T*-cell lymphopenia would identify a **distinct threshold cell count** to differentiate between severe and non-severe infections. We codified an **Index Severity Score** to exploit an association between *T*-cell cytopenia and the grade of disease activity.
Principal result: A *T*-cell count of 560 cells/uL or below signified a trend towards **advanced** disease.
Key findings and conclusions:

(1.) The *T*-cell threshold > 560 cells/uL discriminated 85.7 % **specificity** of the lesser viral infections and <=560 cells/uL identified 100 % **sensitivity** of severe infections or death.
(2.) The **positive predictive value** of this threshold test was 92.9 %.
(3.) *T*-cell apoptosis and sequestration are two of the primary mechanisms of *T*-cell lymphodepletion.
(4.) There is potential for the *T*-cell threshold at <=560 cells/uL to become a **standard** to differentiate disease severity.
(5.) **The T-cell threshold should be tested further against flow cytometry of CD4+, CD8+ counts of individual patients**.
(6.) Future research should explore correlations between the *T*-cell threshold, **medical outcomes** of treatment, Cytokine Release Syndromes, cytokine levels, inflammatory and coagulation markers.

1. Introduction

We made a new synthesis of *T*-cell biomarkers compiled from selective publications to determine if the degree of lymphocytopenia correlated with the severity of coronavirus and influenza A virus (IAV) infections. Our investigation was built upon earlier reports but introducing an **Index Severity Score (ISS)** to systematically grade infections categorized as **(1.)** low-intermediate severity versus **(2.)** severe or death.

We were interested in a two-tiered approach to the investigation of *T*-cell leukopenia associated with coronavirus and IAV infections. These were: **(1.)** an assessment of the total *T*-cell count correlated to the infection severity; **(2.)** determination if a depleted *T*-cell count at a distinct threshold or below would be predictive of escalating infection.

2. Epidemiology

In the unvaccinated, we have the escalated risk of hospitalizations and deaths linked to coronavirus and influenza viruses [1–3]. As of June 2022, the coronavirus cumulative total reportable cases in the U.S. were 87,759,180 with 1,037,664 having died, a consequential 1.12 % mortality rate [4]. The U.S. seasonal influenza rates estimated in 2017–2018 were 41,000,000 illnesses and 52,000 related deaths, a 0.127 % mortality rate [5]. Comparatively, coronavirus had an 8.82-fold higher mortality rate against seasonal influenza but nonetheless, both viruses carried a substantial disease burden.

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3. Methods

In patients infected with either coronavirus or influenza viruses, the *T*-cell subset data were systematically abstracted from 11 medical publications involving 12 studies, a balanced approach including 50 % coronavirus and 50 % IAV studies as summarized in Table 1 **(Results)**. The relevant studies were selected by a key word search of the literature involving such terms as *T*-cell lymphocytopenia, leukopenia, lymphopenia, leukodepletion and lymphodepletion. To be included in our study, it required the inclusion of absolute T- cell subset counts determined by flow cytometry and categorized by disease severity. In the pre-SARS-CoV-2 period, the availability of *T*-cell data was rather limited, abstracted primarily from pertinent studies in east-Asia but the information subsequently becoming prevalent. The associated degree of *T*-cell lymphocytopenia and disease severity were catalogued in Table 2, including 12 studies of infected patients. Three studies were specific to 2019 SARS-CoV-2; three 2002–2003 SARS-CoV-1; four 2009 H1N1 Swine influenza; one 2016–2019 H1N1 Swine influenza; and one 2013 H7N9 Avian influenza.

The absolute CD4+ and CD8+ counts and CD4+/CD8+ ratios and total sum(CD4+:CD8+) *T*-cell count/uL (equivalent terminology **TTCC**) graded the degree of lymphodepletion. The rationale for the TTCC was that while both CD4+ and CD8+ declined with infection, this mixed suppression tended to be primary in one *T*-cell subtype and aggregation would be a better indication of the total degree of lymphopenia. A *meta*-analysis was beyond the scope of our investigation.

As illustrated in the schematic of the **Graphical abstract,** the *T*-cell CD4+ and CD8+ counts in Table 1 were subsequently analyzed in Table 2 incorporating a new ISS scoring system of infection severity**.** It reflected a synthesis of *T*-cell differential counts with five emphases: **(1.)** *T*-cell lymphopenia contrasted against a reference standard, normal cell counts, the controls; **(2.)** quantification of *T*-cell lymphocytopenia that characterized severely infected patients; **(3.)** prediction of escalated infection risk guided by the *T*-cell count; **(4.)** utilization of the CD4+/CD8+ ratio to distinguish either **primary** CD4+ or CD8+ depletion; **(5.)** recognition of disparities regarding *T*-cell subtype depletions.

Standard reference ranges for normal *T*-cell counts are commonly enumerated as a bracketed range without reporting the **mean** values. In Table 1 **section (i.)**, we listed the normal mean *T*-cell counts abstracted from three international studies. In Table 2, we incorporated ISS grading to interpret the degree of *T*-cell lymphopenia against disease severity. An ISS = 1 connoted milder to intermediate grade illness while an ISS = 2 characterized severe illness such as advanced pneumonia, acute respiratory distress syndrome (ARDS), being ICU dependent, prolonged hospitalization or death.

When published statistics were available, we incorporated (std. dev.), (range) and (interquartile range IQR) statistics for CD4+, CD8+ and CD4+/CD8+ ratios in Table 1 and **section 4.** Published CD4+/CD8+ ratios were always recorded but if non-available, these were calculated based upon the CD4+ and CD8+ counts; and additionally, we aggregated by summation CD4+ and CD8+, the total T-cell counts. The compelling advantages in aggregating the *T*-cell data have been elucidated in **section 5.3** and outweighed the limitations of the data and statistics, which have been discussed in **section 5.4**.

4. Results

4.1. Valiathan 2014, Uppal 2003, Bofill 1992. Normal mean T-cell subset values in Western, European and South Asia populations

Spanning a period of 22 years, three cohort studies identified in Table 1 **section (i.)** reported the flow cytometry data for normal mean CD4+ and CD8+ cell counts [6–8]. The results were collected internationally from the United States, India and the United Kingdom involving disparate subject populations. We enumerated the mean (std. dev.) counts in non-lymphopenic persons for the Valiathan and Bofill publications or the 95 % confidence interval ranges (CI) reported in the Uppal publication. In our averaging of the subset data, the normal *T*-cell values being CD4+ 900 cells/uL, CD8+ 568 cells/uL, sum(CD4+:CD8+) 1468 cells/uL and CD4+/CD8+ ratio 1.59.

4.2. Luo 2020. T-cell depletion correlated with survivorship, SARS-CoV-2, China

In a retrospective study Table 1 **section (ii.),** pronounced total *T*-cell depletion occurred among the non-survivors at median 342 cells/uL compared to the survivors at 572 cells/uL [9]. An escalated CD4+/CD8+ ratio of median (IQR) 2.37 (1.77–3.36) among those that had died distinguished greatest decline in CD8+ cells. While survivors were classified overall as having lesser infections ISS=1, this pool of patients could be mixed by some with severe infection, ISS=2.

4.3. Tang 2020, China. T-cell counts in ICU patients infected with SARS-CoV-2 or H1N1 IAV

In Table 1 **section (iii.)**, admission *T*-cell counts median (IQR) regarding CD4+ and CD8+ cells, CD4+/CD8+ ratios and advanced lymphopenia were reported in 148 total ICU patients with ARDS consequent to SARS-CoV-2 or H1N1 IAV [10]. The total *T*-cell count for the SARS-CoV-2 patients was 167 cells/uL (in-hospital mortality 28.8 %) and 274 cells/uL for the H1N1 patients (in-hospital mortality 34.7 %). The median (IQR) was indeterminate for the aggregated total counts.

4.4. Jiang 2020, China. T-cell counts in SARS-CoV-2 ICU and non-ICU patients

In a study of 103 SARS-Cov-2 patients Table 1 **section (iv.)**, an effort was made to discriminate 17 ICU versus 86 non-ICU patients by *T*-cell biomarkers [11]. A data compilation revealed a pronounced *T*-cell lymphopenia linked to ICU admissions. Markedly depleted CD8+ counts were associated with an inflated CD4+/CD8+ ratio of 2.30 and a lesser parallel declination in the CD4+ counts. The *T*-cell counts described either mean (std. dev.) or median (IQR) but not otherwise specified and the actual (std. dev.) and (range) data were unpublished. The calculated TTCC of 342 cells/uL was the reported risk value to distinguish the ICU patients. The severity of infection was well correlated in a ROC graphical plot with an AUC of 0.8810, $p < 0.0001$.

4.5. Shen 2014, China. T-cell counts and H7N9 influenza A

In 2013, an outbreak of an avian origin IAV H7N9 occurred manifested by pneumonia, ARDS, shock and a case fatality rate of 32.1 %. The mean (std. dev.) *T*-cell data were obtained at hospital admission and compiled in Table 1 **section (v.)**. The intensity of infections amplified across two groups from A to B in that order by the excess duration of hospitalizations and/or the occurrence of fatal cases in the later [12]. For the purpose of ISS = 1 scoring and given a period of hospitalization <=40 days in group A, the data pool was mixed by some patients with lengthier hospitalizations that could have been categorized as ISS = 2 infections. Notwithstanding this limitation and while no P values were given, qualitative comparison of the two groups was consistent with a pronounced worsening of total *T*-cell lymphopenia from 450 to 222 cells/uL. This was concordant with a serial progression of the CD4+/CD8+ ratio from 2.15 to 3.00 and CD8+ suppression.

4.6. Fox 2012. Origin 2009 H1N1 Swine influenza A virus in Vietnam and quantification of T-cells to discriminate disease severity

In Table 1 **section (vi.)**, *T*-cell counts were summarized of 49 adult infected cases of Swine Flu hospitalized at the National Hospital of Tropical Diseases in Vietnam [13]. Abnormal physiological parameters of tachypnea, tachycardia and hypoxemia signalized severe illness.

Table 1
Results.

(i.) Valiathan 2014, Uppal 2003, Bofill 1992

a. Normal mean values, CD4+ and CD8+ cell counts per uL Three cohort studies	***Normal *T*-cell Counts (Control) CD4+**	**CD8+**	**CD4+/CD8+ ratio**
(1) USA 2014; N = 100 adults.	1004 (305)	591 (228)	1.8 (0.6)
(2) India 2003; N = 94 adults.	865 (430–1740)	552 (218–1396)	1.7 (0.39–3.02)
(3) United Kingdom 1992; N = 600 adolescents and adults.	830 (288)	560 (231)	1.51 (1.50)
b. Averaging the reported means for CD4+ and CD8+, over the three studies.	900	568	
c: Normal mean CD4+/CD8+ ratio.	1.59		
d. Total of the means, sum(CD4+:CD8+).	1468		

e. Single values in parentheses (std. dev.).
f. Range in parentheses (95 % Confidence interval CI).
***e. Non-lymphopenic persons.**

(ii) Luo 2020

	SARS-CoV-2 Survivors N = 817	**Non-survivors N = 201**	**P Value**
***CD4+ cells/uL**	368 (242–543)	245 (162–318)	<0.001
***CD8+ cells/uL**	204 (143–313)	97 (61–140)	<0.001
CD4+/CD8+ ratio	1.70 (1.30–2.21)	2.37 (1.77–3.36)	<0.001
Total sum(CD4+:CD8+) cells/uL	572	342	

a. N = 1018 hospitalized adults Wuhan, China.
***b. Data represented medians and interquartile ranges (IQR).**

(iii.) Tang 2020

	SARS-CoV-2 *Admissions; ARDS N = 73	**H1N1 **Admissions; ARDS N = 75**
*****CD4+ cells/uL**	97 (57–194)	185 (119–299)
*****CD8+ cells/uL**	70 (36–116)	89 (58–150)
CD4+/CD8+ ratio	1.6 (1.0–2.3)	2.2 (1.5–2.8)
Total sum(CD4+:CD8+) cells/uL	167	274
In-hospital mortality	28.8 %	34.7 %

***a. 73 adult ICU admissions Wuhan, SARS-CoV-2 ARDS out of 179 total admissions infected with SARS-CoV-2, 2019–2020.**
****b. 75 adult ICU admissions Beijing, H1N1 IAV ARDS out of 345 total ARDS pneumonias of various etiologies, 2016–2019.**
*****c. Median values (IQR) at hospital admission.**
d. Adherence to the Berlin criteria ARDS.

(iv.) Jiang 2020

	SARS-CoV-2 Mild-Moderate Disease N = 86 (non-ICU)	**Severe Disease N = 17 (ICU)**	**ROC Curves AUC**	**P Value**
***CD4+ cells/uL**	239		0.8666	<0.0001
***CD8+ cells/uL**	104		0.8618	<0.0001
CD4+/CD8+ ratio	2.30			
Total sum(CD4+:CD8+) cells/uL	342		0.8810	<0.0001

a. Study patients, China.
***b. Cell counts expressed the mean value (std. dev.) or median (quartile P25, P75) @threshold of severe disease but (std. dev.) and (range) data unpublished.**
c. ROC receiver operating characteristics curve.
d. AUC area under curve, a concordance statistic, Q-stat.

(v.) Shen 2014

	H7N9 Avian Influenza A *Group A (N = 12)	****Group B (N = 6)**
*****CD4+ cells/uL**	307 (168)	166 (90)
*****CD8+ cells/uL**	143 (67)	56 (36)
CD4+/CD8+ ratio	2.15	3.00
Total sum(CD4+:CD8+)	450	222

a. H7N9 IAV of avian origin, China, 2013.
***b. Group A: non-fatal infections, patients recovered within 40 days onset of illness.**
****c. Group B: patients died and/or excess hospitalizations beyond 40 days.**
*****d. Expressed as mean values (std. dev.) @ hospital admission.**

(*continued on next page*)

Table 1 (*continued*)

(vi.) Fox 2012

	H1N1 Swine Origin Influenza A Virus 2009		
	Mild cases N = 39	**Severe cases N = 10**	**P Value**
***CD4+ cells /uL @nadir**	543 (346–901)	261 (53–570)	<0.001
***CD8+ cells/uL @nadir**	324 (203–602)	215 (149–830)	0.196
CD4+/CD8+ ratio @nadir	1.32 (0.83–2.06)	0.92 (0.14–1.50)	0.005
Percentage of patients with a CD4+/CD8+ ratio < 1.0 @admission	<1.0 in 16 % of patients	<1.0 in 70 % of patients	0.002
Sum(CD4+:CD8+) cells/uL	867	476	

a. Adult admissions, N = 49 infected cases originated from Ha Noi, Vietnam, 2009–2010.
b. Tachypnea RPM > 30, hypoxemia SpO2 <=92, tachycardia > 100 distinguished severe from mild illness.
***c. Median (10–90 % range) interim values.**
d. ***T*-cell counts at study enrollment unpublished and non-available.**

(vii.) Wen 2011

	H1N1 Swine Origin Influenza A Virus 2009		
	Mild cases pretreatment N = 7	**Severe cases pretreatment N = 9**	**P value**
***CD4+ cells/uL**	484	290	0.002
***CD8+ cells/uL**	355	226	0.002
CD4+/CD8+ ratio	1.36	1.28	
Total sum(CD4+:CD8+) cells/uL	839	516	
Correlation coefficient analysis of PaO2 versus total sum(T:B) lymphocytes	r = 0.771		<0.001

a. N = 16 adult hospitalized H1N1 pneumonitis patients, China 2009.
b. Pulmonary illness severity was discriminated PaO2 < 60 mm Hg (severe infection) versus PaO2 > 60 mm Hg (mild infection).
c. *T*-cell differential counts were obtained a median of 7 days post-symptom onset and extracted from bar graphs and characterized statistically solely by a paired-samples *t*-test.
***d. (std. dev.) and/or (range) data unreported.**

(viii.) Cui 2010

	H1N1 Swine Origin Influenza A Virus 2009					
	Non-ICU	**ICU**	**P Value**	**Survived**	**Died**	**P Value**
***CD4+ cells/uL**	651 (128–1607)	232 (29–1892)	P < 0.0005	471 (86–1892)	119 (29–391)	<0.0005
***CD8+ cells/uL**	406 (85–1113)	167 (23–1109)	P < 0.0005	307 (44–1113)	87 (23–293)	<0.0005
CD4+/CD8+ ratio	1.60	1.39		1.53	1.36	
Total sum(CD4+:CD8+)	1057	399		778	206	

a. A retrospective study of adult patients N = 68 hospitalized with H1N1 pneumonia in China.
***b. Admission data; undefined if mean or median (range) values.**

(ix.) He 2005

	SARS-CoV-1			
	Non-severe cases 2nd week N = 118	**Severe cases 2nd week N = 68**	**Death 2nd week N = 19**	****P Value**
***CD4+ cells/uL**	419 (303)	257 (179)	170 (104)	<0.05
***CD8+ cells/uL**	319 (244)	185 (118)	133 (88)	<0.05
CD4+/CD8+ ratio	1.39 (0.61)	1.61 (1.09)	1.73 (1.40)	<0.05
Total sum(CD4+:CD8+) cells/uL	738	442	303	

a. Sampling of SARS-CoV-1 patients (N = 271, 122 non-severe, 149 severe) in China 2003.
b: Atypical pneumonia guidelines: severe and non-severe disease were defined by abnormal clinical symptoms, physiological disturbances, chest X-ray infiltrates and organ dysfunction.
***c. CD4+ and CD8+ counts expressed as mean values (std. dev.) at 2.0 weeks post-onset of illness when greatest number of deaths.**
****d. A group comparison between severe and non-severe SARS cases.**

(x.) Li 2004

	SARS-CoV-1			
	Recovered 3rd week N = 25	**Acute 1st week N = 98**	**Healthy**	****P Value**
***CD4+ cells/uL**	700	254	858	<0.0001
***CD8+ cells/uL**	500	258	584	<0.0001
CD4+/CD8+ ratio	1.40	0.98	1.47	

(*continued on next page*)

Table 1 (*continued*)

Sum total (CD4+:CD8+) cells/uL	1200	512	1442
CD4+ cells/uL lowest patient count		43	
CD8+ cell/uL lowest patient count		39	

a. Acutely infected adult patients China; a 2002 SARS-CoV-1 pandemic.
***b. Absolute cell counts expressed as mean values without (std. dev.) or (range) data.**
****c. P values reported for healthy control group compared to patients with acute SARS-CoV-1.**
d. Acute stage patients defined by criteria: symptoms, hypoxia and lung consolidation.
e. Recovered patients defined by WHO criteria 21 days post-illness.

(xi.) Cui 2003	**Healthy Control Blood Donors N = 200**	**SARS-CoV-1 **Infected Patients N = 38**	**P Value**
***CD4+ cells/uL**	910 (190)	270 (150)	<0.001
***CD8+ cells/uL**	650 (200)	290 (200)	<0.001
CD4+/CD8+ ratio	1.4	0.93	
Sum total (CD4+:CD8+) cells/uL	1560	560	

***a. Absolute cell counts expressed as mean (std. dev.) values at enrollment.**
b. SARS-CoV-1 2002 in China.
****c. Hospitalizations N = 20 male, N = 18 female; age range 15–80 years.**

Table 2
Analysis of Results.

A	B	C	D	E	F
Study	**Virus**	***ISS = 1, N = 7 data points **TTCC**	***ISS = 2, N = 13 data points **TTCC**	**Primary *T*-cell depletion**	**Characterization of *ISS**
Luo 2020	SARS-CoV-2	572	342	CD8+	Survivors = 1; non-survivors = 2
Tang 2020	SARS-CoV-2		167	Mixed CD4+ and CD8+	At admission; ***ARDS = 2
Tang 2020	2016–2019 H1N1 IAV		274	CD8+	At admission; ***ARDS = 2
Jiang 2020	SARS-CoV-2		342	CD8+	Threshold of severe disease = 2
Shen 2014	H7N9 Avian IAV	450	222	CD8+	Group A non-fatal = 1; Group B fatal or excessive duration of hospitalization = 2
Fox 2012	2009 Swine H1N1 IAV	867	476	CD4+	Mild cases = 1; Severe cases = 2
Wen 2011	2009 Swine H1N1 IAV	839	516	CD4+	Mild cases = 1; Severe cases = 2
Cui 2010	2009 Swine H1N1 IAV	1057	399	CD4+	Non-ICU = 1; ICU = 2
Cui 2010	2009 Swine H1N1 IAV	778	206	CD4+	Survived = 1; Died = 2
He 2005	SARS-CoV-1	738	442	CD8+	Non-severe cases = 1; Severe cases = 2
He 2005	SARS-CoV-1		303	CD8+	Death = 2
Li 2004	SARS-CoV-1	1200	512	CD4+	Recovered infection = non-assigned; Acute infections = 2
Cui 2003	SARS-CoV-1		560	CD4+	Hospitalized acute infection = 2
Median (IQR) total *T*-cells		**778 (572–867)**	**342 (248–494)**		
Average of two medians for ISS = 1 and 2			**560**		

***a. Index severity score (ISS)**
****b. Total *T*-cell count (TTCC cells/uL)**
*****c. Acute respiratory distress syndrome (ARDS)**

Acutely at admission, there was a predilection for CD4+ *T*-cell lymphopenia and an inverted CD4+/CD8+ ratio < 1.0 in 70 % of severely ill patients (unpublished data). Because the subset *T*-cell counts obtained at study enrollment were unpublished and non-available by table format, we relied upon reported interim CD4+, CD8+ counts, median (10-90 % range). At the critical threshold, the total *T*-cell count decreased markedly by 45.1 % from 867 cells/uL at mild infection to 476 cells/uL at severe infection.

4.7. Wen 2011. Categorization of T-cell counts in mild and severe H1N1 Swine Influenza, China

This was a small 16 patient study of adults hospitalized with the H1N1 Swine Influenza A virus [14]. In Table 1 **section (vii.)**, the study categorized 9 patients with severe disease versus 7 with mild illness. Hypoxemia at a PaO2 < 60 mm Hg defined the threshold of severe disease pre-treatment. The subset CD4+ and CD8+ *T*-cell counts were extracted from bar graphs and their suppression for severe disease were

statistically significant at P = 0.002. The TTCC at 516 cells/uL for severe disease compared to a TTCC at 839 cells/uL for mild disease. As (ste. dev.) and (range) data remained unpublished or indeterminate, the subset CD4+, CD8+ counts and TTCC were not further characterized statistically in this way. Concurrently, there was a declination in the CD4+/CD8+ ratio to 1.28 and a positive correlation coefficient r = 0.771, P = 0.003 between PaO2 and total (B plus T) lymphocytes. Proportionally, lymphocytopenia was associated with hypoxemia at a decreased patient PaO2.

4.8. Cui 2010, China. Comparative T-cell counts for 2009 Swine Origin H1N1 influenza A patients correlated to illness severity

As referenced in Table 1 **section (viii.)**, total T cells and the CD4+/CD8+ ratio were calculated in a cohort of N = 65 adult Swine influenza patients categorized by ICU or survivorship status [15]. *T*-cell lymphopenia was progressively associated with increased disease severity and mortality. Total *T*-cell counts were 1057 cells/uL for non-ICU patients compared to 399 cells/uL in the ICU and 778 cells/uL for survivors against 206 cells/uL that died. The CD4+/CD8+ ratios declined to 1.39 for ICU patients and 1.36 for those that died. For the purpose of ISS classification, while survivors were generally designated as a lesser ISS=1 infection, clearly this pool of patients could be mixed with individuals having severe infection, ISS=2.

4.9. He 2005. T-cell counts associated with a 2003 outbreak of atypical pneumonias, SARS-CoV-1 in China

The Chinese Health Ministry categorized the severity of SARS-CoV-1 illness by using criteria of symptomatology, hypoxia, pneumonic infiltrates, ARDS and multiple-organ dysfunction syndrome (MODS). Lymphocyte subpopulations of 271 laboratory confirmed SARS-CoV-1 cases were enumerated in Table 1 **section (ix.)** [16]. CD4+ and CD8+ cell counts were classified in the categories of non-severe disease (N = 122), severe disease (149) and death (N = 48). The greatest number of deaths occurred two weeks post-onset of symptoms and when the total T-cell counts decreased progressively from 738 cells/uL at the stage of non-severe disease to 442 cells/uL at severe disease to 303 cells/uL at death. The mean (ste. dev.) CD4+/CD8+ ratios rose progressively from 1.39 (0.61) at non-severe disease to 1.61 (1.09) at severe disease to 1.73 (1.40) at death.

4.10. Li 2004. A compilation of T-cell data comparing patients categorized with acute SARS-CoV-1, recovered and healthy controls, China

Epidemiologically, fatality rates of 13.2 %-43.3 % were ascribed to novel SARS [17]. In stratifying 98 sick adult patients serially in Table 1 **section (x.),** the deviations in total *T*-cell counts progressed from 1442 cells/uL (healthy controls); 1200 cells/uL (recovered patients); and 512 cells/uL (acute infections) [18]. At lowest count, the lymphopenia was 82 cells/uL. An inverted CD4+/CD8+ ratio < 1.0 occurred in the acute phase of sickness, specifically 0.98. For the purposes of ISS stratification, recovered patients were not assigned ISS scores.

4.11. Cui 2003. T-cell lymphopenia and SARS-CoV-1, China 2002

Thirty-eight patients were admitted to the medical college in Beijing with SARS, presumably atypical pneumonias, diagnosed according to WHO/CDC criteria [19]. Clinically for the purpose of ISS scoring, the degree of acute infections was classified as severe because these patients were hospitalized with a novel **severe** acute respiratory syndrome. *T*-cell assays were performed at enrollment in advance of any treatment including ribavirin or corticosteroids. Absolute mean (std. dev.) CD4+ and CD8+ counts were catalogued in Table 1 **section (xi.)** for infected patients versus healthy blood donors (controls). A total *T*-cell count of 560 cells/uL and an inverted CD4+/CD8+ ratio 0.93<1.0 highlighted lymphocytopenia associated with severe infection compared to the healthy control 1560, ratio 1.4. The (std. dev) of these latter data were indeterminate. The study control of CD4+/CD8+ ratio 1.4 differed from the control defined internationally, 1.59, **section 4.1**.

5. Analysis of results

5.1. T-cell lymphopenia-associated severe coronavirus and influenza infections, compared to a reference standard, normal counts

The normal total *T*-cell count was enumerated in Table 1 **section (i.)**, TTCC = 1467 cells/uL compared to a median TTCC = 342 cells/uL for **severe infection**, further elucidated in **section 5.2** below. This reflected a profound lymphodepletion effect of infection, a 76.7 % decline in total *T*-cells against normal control values.

5.2. T-cell counts in severe versus non-severe cases of respiratory viral syndromes, an evidence-based analysis

In Table 2, we selected the index severity scores ISS = 1 or 2 to characterize the cases with coronavirus or IAV as defined in Column F. We pooled two groups representing ISS = 2 severe and ISS = 1 non-severe infections; the listing of total *T*-cell counts being extracted from data well-described in Table 1. Column D identified the group of severe cases (N = 13) versus Column C, which demarked the non-severe cases, (N = 7). An overall median (IQR) total *T*-cell count was derived for both groups and being **342** (248–494) cells/uL for ISS = 2 and **778** (572–867) cells/uL for ISS = 1 infections. These values were emboldened, the bottom of Columns D and C respectively. The logic of this statistical approach would become advantageous if in fact it defined a ***T*-cell threshold** which would incriminate a degree of lymphopenia predictive of high-risk infection. Hence, we expanded this concept in **section 5.3** below.

5.3. T-cell counts as a benchmark of advanced respiratory viral illnesses

By averaging the two median TTCC counts for ISS = 1 and ISS = 2 infections previously described in **section 5.2**, we calculated an intermediate value of **560** cells/uL shown in the bottom of Table 2. We applied this *T*-cell threshold to test if predictive of advanced infection. Utilizing a 2 × 2 contingency Table 3, we defined a **positive test for severe infection** of TTCC <=560 cells/uL and a **negative test** TTCC > 560 cells/uL. The contingency table was constructed based upon the categorized TTCC data in Table 2 and most importantly relied upon the index severity scores ISS 1 and 2 to categorize the data.

Our *T*-cell test proved to be quite functional in identifying infection severity based upon an analysis of 20 total *T*-cell counts elicited in 11 publications. We subsequently analyzed that data in the contingency Table 3 which yielded some revelations of import. The *T*-cell threshold of > 560 cells/uL identified lesser infections, scored ISS = 1 in six of the seven applicable *T*-cell counts, an 85.7 % **specificity.** The *T*-cells <=560 identified ISS = 2 severe infections, 13 of the 13 relevant *T*-cell counts, a 100 % **sensitivity**. Given the excellent discriminatory value of TTCC @ 560 cells/uL, in 19 of 20 cases, it correctly distinguished the severity of coronavirus and influenza respiratory illnesses, either ISS = 1 or 2. The **positive predictive value (PPV)** of the test was 92.9 %. Therefore, we have strong evidence that *T*-cell lymphocytopenia <=560 cells/uL would be a promising benchmark defining disease activity and for quantitative analyses of CD4+, CD8+ flow cytometry in individual patients. It has not escaped our attention that as a biomarker of disease activity, if the *T*-cell threshold count were set too high, we run the risk of overtreating non-serious illnesses; and conversely, if we set the *T*-cell threshold count too low, we run the risk of missing progressive infections until too late.

Table 3
2 × 2 contingency table.

		Reference						
		Severe infection	Non-severe infection			Severe infection	Non-severe infection	
	Test cells/uL	ISS = 2	ISS = 1	Total	Test cells/uL	ISS = 2	ISS = 1	Total
	(Pos)<=560	13	1	14	(Pos)<=560	TP[a]	FP[c]	
	(Neg) > 560	0	6	6	(Neg) > 560	FN[d]	TN[b]	
	Total	13	7	20	Total			
True positives	TP	12						
True negatives	TN	7						
False positives	FP	1						
False negatives	FN	0						
	Sensitivity	100 %						
	Specificity	85.7 %						
Positive predictive value	PPV	92.9 %						

a. True positives concurrently have a positive test and severe infection.
b. True negatives concurrently have a negative test and non-severe infection.
c. False positives concurrently have a positive test and non-severe infection.
d. False negatives concurrently have a negative test and severe infection.

5.4. Advantages and limitations in the study methodology and the aggregation of data

5.4.1. Advantages

Despite data imperfections, our approach in aggregating the data was a work around to best identify a discrete total *T*-cell threshold which well-discriminated infection severity against the prevailing medical evidence in 12 of our studies. In that vein, we developed a 2 × 2 contingency table to define the sensitivity, specificity and positive predictive value of the threshold test as described in **section 5.3** above.

5.4.2. Limitations

1. The estimation of the total *T*-cell counts and CD4+/CD8+ ratios involved using a calculated summation of the available median or mean CD4+ and CD8+ counts but not extracted from individual counts, which were non-available, unpublished in the literature. Moreover, dependent upon the predilection of the individual study, we were impeded by the non-uniformity of using either median or mean data sources.
2. The (std. dev.) and (range) data were indeterminate for the total *T*-cell counts, being impossible to extrapolate from the aggregated CD4+ and CD8+ counts.
3. Unless the CD4+/CD8+ ratios were specifically published in the literature with (std. dev.) or (range) information, these were indeterminate. When available, we included the statistics in Table 1.
4. The assignment of ISS scores required some assumptions about illness severity and the idiosyncrasies have been identified where important in **section 4** such as (i.) commingling of data by patients with serious infections while listed in a pool of less severely afflicted individuals; (ii.) lack of uniformity in classification of infection severity by study.
5. The lack of uniformity in reporting the T-cell counts at hospital admission.

5.5. Preferential suppression of T-cell subsets by virus type

Firstly, infected patients with coronavirus or IAV have a known predilection to a mixed lymphopenia and an altered CD4+/CD8+ ratio when one cell type has preferentially been suppressed, the **primary** to another, the secondary. For example, CD8+ is primary for an elevated ratio above the control and CD4+ is primary for a depressed ratio below the control and leading to a ratio < 1.0, termed an **inverted ratio**. This is clearly indicated in Table 1 **section (i.),** listed is the normal control CD4+/CD8+ ratio 1.59, as a representative of the non-lymphopenic population. **Secondly** when the CD4+/CD8+ ratios were cross-referenced across Table 1 to various published studies, by strain of virus, the primary nature of the *T*-cell depletion type varied, as listed in column E, Table 2. For instance, in He 2005, a rising trend in CD4+/CD8+ ratios Table 1 correlated to CD8+ suppression noted in Table 2**,** comparing non-severe, severely infected SARS CoV-1 cases and death in that order; **Thirdly**, in two of three SARS-CoV-2 studies, the depletion of CD8+ cells was primary (66.7 %), Table 2 and mixed cellular suppression, given a CD4+/CD8+ ratio 1.6 close to the control 1.59 (i.e. for Tang 2020). Two of three SARS-CoV-1 studies Li 2004 and Cui 2003 signified primary CD4+ depletion (66.7 %) and He 2005, CD8+ depletion (33.3 %). Hence collectively, there was an inclination towards primary CD8+ depletion in SARS-CoV-2 and primary CD4+ depletion for SARS-CoV-1. Three of four H1N1 IAV studies (75 %) indicated CD4+ suppression, one CD8+ suppression and the one Avian IAV study primary CD8+ cytopenia.

5.6. CD4+/CD8+ depletion disparities

Disparities were noted in Table 2**,** the SARS-CoV-1 CD4+ and CD8+ depletion data. Primary CD8+ depletion was observed in He 2005 against CD4+ depletion, Li 2004 and Cui 2003. Given a single virus type, the biological reason for this variation in *T*-cell suppression was indeterminate but raised the question whether it implicated variability in the strain of the virus.

We reviewed the subsequent 9-year evolution of a different virus, H1N1 IAV. We contrasted the primary CD8+ depletion, the Tang 2020 study in Beijing (2016–2019) to primary CD4+ depletion, the earlier 2009 H1N1 pandemic studies, Table 2. Phylogenetically, the gene sequences of 33 H1N1 pdm09 viruses were analyzed in the later 2015–2017 flu seasons of Beijing, a sampling of 11,112 patients. These analyses significantly reflected the co-occurrence of new mutations arising in the hemagglutinin and neuraminidase genes [20] and occurring in **temporal relationship** to the noted alterations in *T*-cell subtype suppression. Furthermore, the overexpression of cell surface neuraminidase has been correlated experimentally as a cause of pronounced apoptosis of CD4+ and CD8+ cells but indeterminate as to any differential effect ([21] and personal communication with the co-author Roberts NJ on 05–27-2022]. The mechanism of quantifiable neuraminidase overexpression and apoptosis has been further elucidated in **Discussion section 6.6** and would warrant further experimental evidence about CD4+/CD8+ depletion disparities.

6. Discussion

6.1. Rationale for T-cell counts in infection induced leukopenia and pneumonia

In our analysis we have advanced the concept of an infection-based

index severity scoring system to link the *T*-cell count of <=560 cells/uL to characterize the patients at highest risk. We compiled total T-cell counts aggregated from absolute CD4+ and CD8+ counts published in the literature. The data was collated regarding a miscellany of SARS and IAV infections causing leukopenia and pneumonia. Other investigators of these viruses have fostered a similar idea of monitoring the leukocyte characteristic profiles to distinguish patients at risk [15,22,23]. We proposed the T-cell threshold <=560 cells/uL as a benchmark to be tested against the flow cytometry of individual patient CD4+, CD8+ counts.

Of course, we are not insinuating *T*-cell counts as the sole criteria to treat for the purposes of use in the general care of infected patients or clinical trials, recognizing that treatment should be personalized by multiple clinical elements. These are the history and physical examination, the radiology, supported by relevant laboratory findings, including the quantification of *T*-cell differential counts. As an extension to our study of depleted *T*-cell counts, it would be logical to discuss putative mechanisms of *T*-cell viral cytotoxicity. All respiratory viral infections are known to trigger both innate and adaptive immune systems of our physiological defense mechanisms. Innate immunity is manifested as an early response to infection guided by the recruitment of neutrophils, macrophages, dendritic cells and activated complement pathways. Accordingly, within a week into the disease course, B and *T*-cells are activated and through the development of neutralizing antibodies, this being the essential part of human defense mechanisms of the adaptive immunity; and a potential latent *T*-cell cytopenia that would ensue becoming the focus of the subsequent discussion [24,25].

6.2. Theories of T-cell depletion in viral pneumonias

We discuss two primary mechanisms, **(1.)** *T*-cell sequestration and **(2.)** *T*-cell apoptosis of the *T*-cell lymphopenia attendant to viral infections of the coronaviridae and orthomyxoviridae (influenza) phylogenetic families. The supporting evidence is illustrative but may not be generalizable to all the viruses catalogued in Tables 1 and 2.

6.3. Sequestration, the coronaviruses

Aligned with the adaptive immune response associated with SARS-CoV-2/ CoV-1 pneumonias, CD4+, CD8+ *T*-cells have been reported as recruited, trafficked, and trapped in the damaged lung as a cause of *T*-subset lymphocytopenia [16,26,27]. The confirmatory analyses included semi-quantitative immunohistochemistry of an 80 % proportion CD8+ lymphocyte infiltrate sampled at full autopsy or by needle lung biopsy at death [27].

6.4. Sequestration, influenza A viruses

In the mid-1980 s, *T*-cell lymphocytopenia was observed in college students associated with an outbreak of influenza type A/Philippines/2/82 (H3N2) virus [28]. One plausible mechanism for the *T*-cell cytopenia implicated pulmonary sequestration of *T*-cells consequent to cell-mediated immunological reactions of infection in situ. The normal host immune response should be protective by trafficking *T*-cells but has capacity to become immunopathological locally and causal to respiratory disease severity [29]. Dating back earlier to the 1970 s, this concept had been explored experimentally in murine models of influenza A/Hong Kong H3N2 using techniques of transpleural lavage and quantitative lymphocytic immunofluorescent assays [30]. The study confirmed increased *T*-cell leukocytes in the lungs of infected mice.

6.5. Invasive coronaviruses: T-cells and apoptosis

Direct SARS-CoV-2 invasion to the cell has been associated with *T*-cell cytopathy, *T*-cytopenia, systemic inflammation and a diminished clinical prognosis [31–33]. *T*-cell dysfunction has been ascribed to *T*-virus induced apoptosis, hypercytokinemia IL-10/TNF-α, nicotinamide adenine dinucleotide (NAD+) depletion related to CD38 overexpression, concurrent ATP depletion, and dysregulation of the Surtuin proteins which influence *T*-cell durability and death [26,34–36].

In fact, recently in 2020, CD147 was proposed to facilitate invasive SARS-CoV-2 into the human host CD4+ and CD8+ cells [31]. CD147 is a transmembrane glycoprotein known as EMMPRIN/ basigin encoded by the BSG gene [37,38]. Heretofore in early 2005, HAb18G/CD147 was first linked to the invasion of SARS-CoV-1 in a human kidney epithelial cell line [39]. In the subsequent 2020 research, it merited notice the existence of ACE2 and CD147 as dual auxiliary co-receptors acting as co-conspirators to propagate SARS infections independently [31]. ACE2 was previously established in 2003 as a functional receptor for SARS-CoV-1 and subsequently in 2020 for SARS-CoV-2 [40,41]. Moreover, the ACE2 receptor has wide distribution in organs: respiratory, hepatic, myocardial, urological and gastrointestinal to impact diverse pathology by infection [42–43]. The ACE2 receptor in lung is downregulated by SARS-CoV-2 infection, and the viral infection perturbs the renin-angiotensin system, propagates pulmonary edema and contemperaneously hijacks CD147 [31].

Furthermore *T*-cells harvested from the lung of a SARS-CoV-2 infected patient in China were deficient in the expression of ACE2 for docking of coronavirus; and based upon study about CD147 and SARS in 2005, an alternate pathway was proposed of SARS-CoV-2 viral invasion [31,39]. This was supported by immuno-electron microscopy and immunofluorescence confirming the co-localization of a CD147-SARS-CoV-2 spike complex and corona virions inside immune *T*-cells. In addition, to simulate a mechanism of viral cellular invasion, sequential endocytosis of the CD147-spike complex for SARS-CoV-2 was modeled in Simian Vero E6 cells and confirmed by electron microscopy [31].

6.6. Influenza A virus and T-cell apoptosis

Apoptosis of human lymphocytes exposed to IAV was studied experimentally in 2001 by Nichols et al. [44]. Cell death was induced by cross linkage of tumor necrosis proteins expressed molecularly on the cell surface identified as Fas, a 48-kDa transmembrane CD95 death receptor and FasL, a 40-kDa Fas ligand. IAV induced cytokinemia, activated monocyte/macrophage CD14 cells and increased the density of Fas/FasL expression on CD3 and mature CD4+/CD8+ cells [45]. The Fas/FasL in turn activated caspase-3 and protease caspases downstream to control cytoplasmic and nuclear events of apoptosis [45,46].

Pronounced apoptosis of CD3 *T*-cells was elucidated in a 2019 sequel paper by Nichols et al. They assayed multiple strains of human IAV infectivity of human monocyte/macrophages and quantified over-expression of cell surface neuraminidase (NA), an inducer of CD3 caspase-3 executioner promoter and apoptosis [21]. Concurrent death of mature circulating CD4+ and CD8+ cells would be explainable related to the known co-expression of the CD3 marker on these same cells.

6.7. Future perspectives on the essential roles of cytokines and inflammatory markers in severe infections

Previously, we surveyed 11 publications, all of which reported various aspects of *T*-cell differential counts. These were summarized concisely in our tables, eliciting a principal *T*-cell threshold of <=560 cells/uL as a critical predictor of advancing infection. Subsequently, we performed an additional analysis of reported quantitative biomarkers of infection-induced hyper-inflammation. However, in view of the limited reporting in these targeted papers (interleukins levels mentioned only in 30 %, chemokines in 20 % and inflammatory markers such as C-reactive protein in 40 %), it is warranted a further in-depth systematic analysis to interpret the evidence. The principal goal would be to evaluate the clinical significance of the total *T*-cell counts and levels of inflammatory mediators concurrently and correlated in conjunction to disease activity. In the context of pronounced leukocytopenia and hyperinflammation

that are acting adversely in concert, novel therapeutic strategies should be introduced and tested to measure medical outcomes.

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.

Data availability

The data is in Tables 1 and 2, Excel files. If we go to R1, these files can be adapteed to MSWord docs

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