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Low interferon-gamma release in response to phytohemagglutinin predicts the high severity of diseases

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Abstract

A clinically useful immune biomarker could potentially assist clinicians in their decision making. We stimulated T-cell proliferation to secret interferon gamma (IFN-γ) by phytohemagglutinin, and then measured the production of IFN-γ (mitogen value [M value]). We aimed to determine the relationship between the M value, clinical severity, and outcomes of diseases.

In all, 484 patients admitted to intensive care units were enrolled in this retrospective study. The Acute Physiology and Chronic Health Evaluation II (APACHE II) scores were collected within the first 24 hours. M value, C-reaction protein (CRP), procalcitonin (PCT), erythrocyte sedimentation rate (ESR), and routine blood tests were analyzed and collected during the study.

When APACHE II scores were greater than 15 and M values were less than 6, the hospital mortality rose in a straight line. There was an inverse correlation between APACHE II score and M value ($r_s = -0.212$, $P < .001$). There was a positive correlation between M value and lymphocyte numbers ($b' = 0.249$, $P < .001$); however, there was an inverse correlation between M value and WBC ($b' = -0.230$, $P < .001$), and ESR ($b' = -0.100$, $P = .029$). Neurological diseases had the greatest influence on APACHE II scores ($b' = 10.356$, $P < .001$), whereas respiratory diseases had the greatest influence on M value ($b' = 1.933$, $P < .001$). Furthermore, in the respiratory system, severe pneumonia had a greater influence on M value. Taking the APACHE II score as the gold standard, the area under the curve of M was 0.632 (95% confidence interval [CI] 0.575–0.690, $P < .001$), PCT was 0.647 (95% CI 0.589–0.705, $P < .001$), CRP was 0.570 (95% CI 0.511–0.629, $P = .022$), and ESR was 0.553 (95% CI 0.494–0.612, $P = .078$). Divided by M value = 5, the positive predictive value of the M value is 37.22% (115/309) and negative predictive value is 75.43% (132/175).

The results show that the M values, PCT, and CRP were better than ESR to predict the severity of diseases. The number and proportion of lymphocytes also affected the result of the M value. To a certain extent, the M value may be a clinically useful immune biomarker, which may help clinicians objectively evaluate the severity of diseases, especially in the respiratory system.

Abbreviations: AECOPD = acute exacerbation of chronic obstructive pulmonary disease, AIDS = acquired immune deficiency syndrome, APACHE II = Acute Physiology and Chronic Health Evaluation II, CA = cancer, CRP = C-reaction protein, DRGs = diagnosis-related groups, ELISA = enzyme-linked immunosorbent assay, ESR = erythrocyte sedimentation rate, ICU = intensive care unit, LODS = Logistic Organ Dysfunction Score, LY = lymphocyte, M tube = mitogen tube, MODS = Multiple Organ Dysfunction Score, MOF = multiple organ failure, MPM = Mortality Prediction Model, NPV = negative predictive value, PCT = procalcitonin, PHA = phytohemagglutinin, PPV = positive predictive value, QFT-GIT = Quantiferon-TB Gold In-Tube, ROC= receiver-operating characteristic, SAPS = Simplified Acute Physiology Score, SOFA = Sepsis-related Organ Failure Assessment Score, TB = tuberculosis, WBC = white blood cell.

Keywords: APACHE II score, diseases severity, immune biomarker, interferon gamma, phytohemagglutinin

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1. Introduction

Humans are at risk from many pathogenic viruses, bacteria, fungi, and parasites, even as the innate and adaptive immune systems have matured.[1] Patients with sepsis can display suppressed immune function. Various immune cell populations reduce significantly during sepsis, and the remaining lymphocyte function is also decreased. They often manifest as an increased susceptibility to nosocomial infections and high mortality.[2] Commensal microbiota-derived metabolites inhibit histone deacetylases to induce regulatory T cells, whereas some infectious agents induce DNA methylation. These data imply that epigenetic regulation of host defense cells, which are usually the first to encounter external antigens, are implicated in disease development.[3]

There are many scoring systems to describe the degrees of organ dysfunction and evaluation of morbidity in intensive care unit (ICU) patients. The severity of diseases was evaluated according to important symptoms, physical signs and physiological parameters of the disease. There are many scoring systems such as Acute Physiology and Chronic Health Evaluation (APACHE) II, III and IV, Simplified Acute Physiology Score (SAPS), Mortality Prediction Model (MPM), Multiple Organ Dysfunction Score (MODS), Sepsis-related Organ Failure Assessment Score (SOFA), Logistic Organ Dysfunction Score (LODS), and so on.[4,5] APACHE II includes an acute physiology score, age points, and chronic health points.[6] Within the first 24 hours of patient admittance, the worst value for each physiological variable is calculated into an integer score ranging from 0 to 71. Higher scores represent a more severe disease and a higher hospital mortality risk. The APACHE II is the most commonly used severity-of-disease scoring system around the world, and is currently used in clinical practices.[7] Additionally, documentations were dependent on its levels, so we chose APACHE II to assess the severity of diseases.

Nonetheless, these scoring systems are complicated and cannot predict the immune status of patients. A clinically useful immune biomarker could potentially assist clinicians in their decision-making.

Quantiferon-TB Gold In-Tube (QFT-GIT) kits are used to diagnose the tuberculosis (TB) infection, which has been selected for the standardization operation diagram in the China TB laboratory.[8] It is a simple in vitro interferon gamma (IFN-γ)-releasing functional assay, which measures whole blood T-cell activity without the need for peripheral blood mononuclear cell isolation. It has a positive care coating phytohemagglutinin (PHA) called mitogen tube (M tube). PHA stimulated T-cell proliferation to secrete IFN-γ, and then we measured the production of IFN-γ (the result was named M value) to reflect the proliferation function of T cells. This study explored the factors that affected the function of T cells by analyzing the relationship between M values and clinical indicators. We used APACHE II as the gold standard to explore whether the M value could predict the severity of disease or not.

2. Materials and methods

2.1. Study population and procedures

We conducted a retrospective study of patients who were admitted to the ICU in The First People's Hospital of Qujing City in Yunnan Province between April, 2017 and May, 2018. The ICU in our hospital was divided into 6 departments, including respiratory ICU, neurology ICU, neurosurgery ICU, cardiology ICU, emergency ICU, and center ICU. The patients with a clear diagnosis were assigned to the corresponding ICU directly, whereas the patients with an unclear diagnosis were assigned to the emergency ICU. The center ICU was mainly responsible for patients with multisystem involvement, multiorgan failure, and severe infection.

Patients were consecutive adults (age >16 years old). For each patient, the following data were obtained: APACHE II scores, M value, blood routine test, C-reaction protein (CRP), erythrocyte sedimentation rate (ESR), and procalcitonin (PCT). Patients were grouped into 7 categories: Respiratory system diseases (376), digestive system diseases (25), nerve system diseases (11), urinary system diseases (6), acquired immune deficiency syndrome (AIDS) (13), ICU severe infection (22), and other causes (31). ICU cases involving severe infection contained bacteremia (1), septicemia (3), sepsis (8), septic shock (4), multiple organ failure (MOF) (5), and cachexia (1). Surgery patients were not admitted. For patients with multiple diagnoses, we applied the diagnosis-related groups (DRGs) system to determine the first diagnosis for the patients, and the criteria were unified throughout the hospital. The first diagnosis for the patients was selected as the main reason for admission.

2.2. Ethics statement

All human experiments performed were approved by Institutional Human Ethics Committee of the First People's Hospital of Qujing City in Yunnan Province and were consistent with the principles outlined in NIH guidelines on the ethical conduct of human research. This was a retrospective study of routinely collected data, so informed consent was not required by our ethics committee. Anonymous patient information was obtained from the hospital's electronic patient database.

2.3. Laboratory procedures

Blood (1 mL) in heparin tubes was transferred to mitogen tubes (M value), and incubated at 37°C for 16 to 24 hours. After incubation, the samples were returned to ambient room temperature and centrifuged at 3000 g for 15 minutes, and then the plasma was extracted. Enzyme-linked immunosorbent assay (ELISA) was performed to measure the parameters. The ELISA plate was read at wavelengths of 450 and 630 nm. Data were transferred to the QFT-Plus analysis software to calculate results. APACHE II, M value, CRP, ESR, PCT, and routine blood tests were calculated 24 hours after admission to the medical ward.

2.4. Statistical analyses

Data were expressed as medians and ranges or numbers (percentages), mean ± SD, and mean ± Q. For comparison in different groups, analysis of variance for normal distribution data and Kruskal-Wallis for skewed data were performed.[9] Logistic regression[10] was used to analyze the relationship between APACHE II and survival outcome, and also the relationship between M value and survival outcome. Spearman rank correlation was applied to analyze the correlation between different APACHE II groups and mortality, and to analyze the correlation between different M value groups and mortality. Multiple linear regressions were used to analyze the relationship between APACHE II and M value in various system diseases, and also the relationship between M value and clinical indicators. Statistical analyses were performed using SPSS software (version 17.0). Meaningful *P* values were different in different statistical methods.

3. Results

3.1. Participant demographics and PHA responses predicted survival outcomes

In all, 484 patients were included in the study; 330 patients were male (68.2%) and 17 patients (3.5%) died. The mean age for all patients was 61.27 ± 17.25 years (range 18–101). The mean age for males was 61.71 ± 17.40 years and for females was 60.34 ± 16.95 years. The age difference was not statistically significant ($P = .416$). There was not a statistically significant difference between the mean age of survivors (61.05 ± 17.23) and nonsurvivors (68.13 ± 17.15) ($P = .118$).

We also observed the changes of M values in different groups. M values were significantly different in the overall comparison ($x^2 = 37.271$, $P < .001$). Compared with the control group (APACHE II [0–4] group), the differences of M values in the 4 groups with APACHE II ≥15 were statistically significant ($P < .008$, the test level needed to be adjusted for multiple pair-wise comparisons of data, inspection level α' = inspection level α/times of comparing) (Table 1). We also analyzed the correlation between APACHE II and M values. After APACHE II grouping, there was a weak and direct significant inverse correlation between APACHE II scores and M values ($r_s = -0.212$, $P < .001$) (Fig. 1A). The relationship between APACHE II scores and hospital mortality was also analyzed.

Patient survival outcome was the dependent variable. In the regression model, only APACHE II and M value entered the equation, and other variables such as CRP, ESR, and PCT were eliminated. The risk of death was 1.194 times higher for each additional unit of APACHE II score (odds ratio [OR] 1.194, 95% confidence interval [CI] 1.073–1.329, $P < .05$). There was a positive correlation between APACHE II score and hospital mortality ($r_s = 0.964$, $P < .001$). The hospital mortality rose linearly when APACHE II scores were ≥15 (Fig. 1B). We further assessed the relationship between M values and hospital mortality. Death occurred when M values were <6. The lower the M values, the higher the hospital mortality. However, there was no significant correlation between M values and hospital mortality (OR 0.479, $P = .055$) (Fig. 1C).

3.2. The correlation between M values and clinical indicators

Clinical indicators were significantly different in the overall comparison except in the platelet group (Table 2). Compared with the M values (0.00–2.99) group, the difference was statistically significant when $P < .017$ (Table 2). On multiple linear regression analyses, entry criteria $\alpha = 0.05$, elimination criteria $\beta = 0.10$, and M values had a linear relationship with white blood cell (WBC), lymphocyte (LY), and ESR. M values were positively correlated with LY ($b' = 1.089$, $P < .001$), but negatively correlated with WBC ($b' = -0.120$, $P < .001$) and ESR ($b' = -0.009$, $P = .029$). These results indicate that the more serious the disease, the lower numbers of LY and LY%, and also the lower IFN-γ released to PHA. When WBC and ESR tended to be normal, IFN-γ tended to release normal levels (Table 2). Taking APACHE II score as the "gold standard," APACHE II scores ≥15 were divided into a serious group, and APACHE II scores <15 were divided into a light-medium group. The receiver-operating characteristic (ROC) curve was made to study the M values, PCT, CRP, and ESR as a way to predict the severity of diseases (Fig. 2). The area under the curve of M was 0.632 (95% CI 0.575–0.690, $P < .001$), PCT was 0.647 (95% CI 0.589–0.705, $P < .001$), CRP was 0.570 (95% CI 0.511–0.629, $P = .022$), and ESR was 0.553 (95% CI 0.494–0.612, $P = .078$). The results show that the M values, PCT, and CRP were better than ESR in predicting the severity of diseases. Divided by M value = 5, the positive predictive value (PPV) of the M value is 37.22% (115/309) and negative predictive value (NPV) is 75.43% (132/175).

Table 1

Participant demographics (n = 484).

APACHE II	Male, n (%)	Median age, y (mean ± SD)	M values (mean ± SD)
0–4 (n = 73)	42 (57.53)	39.11 ± 12.63	4.99 ± 2.93
5–9 (n = 123)	79 (64.23)	56.16 ± 13.87	4.21 ± 3.09
10–14 (n = 130)	92 (70.77)	66.71 ± 13.30	4.41 ± 3.04
15–19 (n = 112)	80 (71.43)	71.51 ± 12.79	3.82 ± 3.00*
20–24 (n = 27)	20 (74.07)	72.00 ± 15.13	2.15 ± 2.32*
25–29 (n = 12)	11 (91.67)	64.75 ± 15.46	2.12 ± 2.86*
30–34 (n = 7)	6 (85.71)	70.14 ± 11.63	1.29 ± 1.10*

APACHE II = Acute Physiology and Chronic Health Evaluation II, M value = mitogen value, the production of IFN-γ.

* Compared with the APACHE II (0–4) group, $P < .008$ was statistically significant ($P < .008$, the test level needed to be adjusted for multiple pair-wise comparisons of data, inspection level α' = inspection level α/times of comparing).

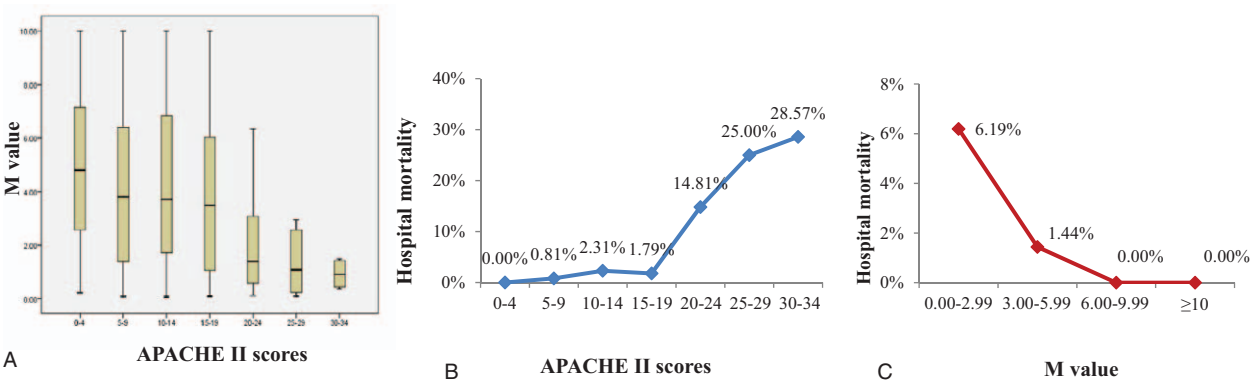

Figure 1. The correlation between M value and APACHE II scores, and PHA responses predicted survival outcomes. (A) After APACHE II grouping, there was a weak and direct significant inverse correlation between APACHE II scores and M values ($r_s = -0.212$, $P < .001$). (B) The hospital mortality rose linearly when APACHE II scores were ≥15. (C) Death occurred when M values were <6. There was no significant correlation between M values and hospital mortality (OR 0.479, $P = .055$). APACHE II = Acute Physiology and Chronic Health Evaluation II, OR = odds ratio, PHA = phytohemagglutinin.

Table 2

The correlation between M value and clinical indicators.

M value	WBC (mean ± Q)	LY (mean ± Q)	LY (%) (mean ± Q)	HCT (mean ± Q)	PCT (mean ± Q)	CRP (mean ± Q)	PLT (mean ± SD)	ESR (mean ± SD)
0.00–2.99 (n = 210)	8.50 ± 9.27	0.83 ± 0.69	9.30 ± 13.55	0.37 ± 0.08	0.26 ± 2.13	96.50 ± 165.40	247.61 ± 146.27	58.57 ± 33.00
3.00–5.99 (n = 140)	8.30 ± 5.45	1.22 ± 0.80*	13.50 ± 11.65*	0.39 ± 0.10*	0.10 ± 0.34*	89.28 ± 166.18	269.23 ± 128.11	52.71 ± 29.61
6.00–9.99 (n = 100)	7.15 ± 4.18*	1.20 ± 0.74*	16.70 ± 11.85*	0.43 ± 0.10*	0.10 ± 0.30*	60.38 ± 127.11*	248.95 ± 118.69	45.19 ± 31.43*
≥10 (n = 34)	6.50 ± 2.70*	1.80 ± 0.81*	28.90 ± 15.32*	0.44 ± 0.05*	0.10 ± 0.00*	10.50 ± 37.45*	207.29 ± 70.19	25.06 ± 24.17*
Total χ^2	14.996	65.159	73.430	46.715	26.755	43.285	5.852	36.088
P	.002	<.001	<.001	<.001	<.001	<.001	.119	<.001

CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, HCT = hematocrit, LY = lymphocyte, PCT = procalcitonin, PLT = platelet, WBC = white blood cell.

* Compared with the M value (0.00–2.99) group, $P < .017$ was statistically significantly different ($P < .017$, the test level needed to be adjusted for multiple pair-wise comparisons of data, inspection level α' = inspection level α/times of comparing).

3.3. The relationship between APACHE II scores and M values in various systemic diseases

In the overall comparison, APACHE II scores ($x^2 = 27.569$, $P < .001$) and M values ($x^2 = 40.622$, $P < .001$) in different system diseases were different in regards to statistical significance. Compared with the respiratory system diseases, $P < .05/6$ was significantly different (Table 3). On multiple linear regression analyses, entry criteria $\alpha = 0.05$, elimination criteria $\beta = 0.10$, APACHE II had linear relationships with respiratory system diseases ($b' = 2.577$, $P = .002$), nervous system disease ($b' = 10.356$, $P < .001$), urinary system diseases ($b' = 7.841$, $P = .004$), and ICU severe infection ($b' = 6.174$, $P < .001$). The standard partial coefficient predicted that neurological diseases had a greater impact on APACHE II scores (Table 3). M values had a linear relationship with respiratory system diseases ($b' = 1.933$, $P < .001$), whereas respiratory system diseases had a greater impact on M values (Table 3).

3.4. The relationship between APACHE II and M values in respiratory system diseases

In respiratory system diseases, APACHE II scores ($x^2 = 163.240$, $P < .001$) and M values ($x^2 = 48.829$, $P < .001$) were significantly different in the overall comparison. Compared with severe pneumonia, $P < .006$ was significantly different (Table 4). There was a weak and direct significant inverse correlation between APACHE II scores and M values ($r_s = -0.222$, $P < .001$), regardless of the APACHE II group or M value group in respiratory system diseases (Table 4).

On multiple linear regression analysis, entry criteria $\alpha = 0.05$, elimination criteria $\beta = 0.10$, APACHE II had a linear relationship with severe pneumonia ($b' = 3.120$, $P < .001$), acute exacerbation of chronic obstructive pulmonary disease (AECOPD) ($b' = 4.167$, $P < .001$), bacterial pneumonia ($b' = -4.514$, $P < .001$), and TB ($b' = -5.767$, $P < .001$). The standard partial coefficient predicts that AECOPD had a greater impact on APACHE II scores (Table 5). M values had a linear relationship with severe pneumonia ($b' = -2.554$, $P < .001$), pulmonary abscess ($b' = -3.153$, $P = .001$), and lung CA ($b' = -1.781$, $P = .029$). The standard partial coefficient predicts that severe pneumonia had a greater impact on M values (Table 6). APACHE II scores might predict the severity of disease, especially AECOPD. At the same time, M values might predict the severity of diseases, particularly on severe pneumonia.

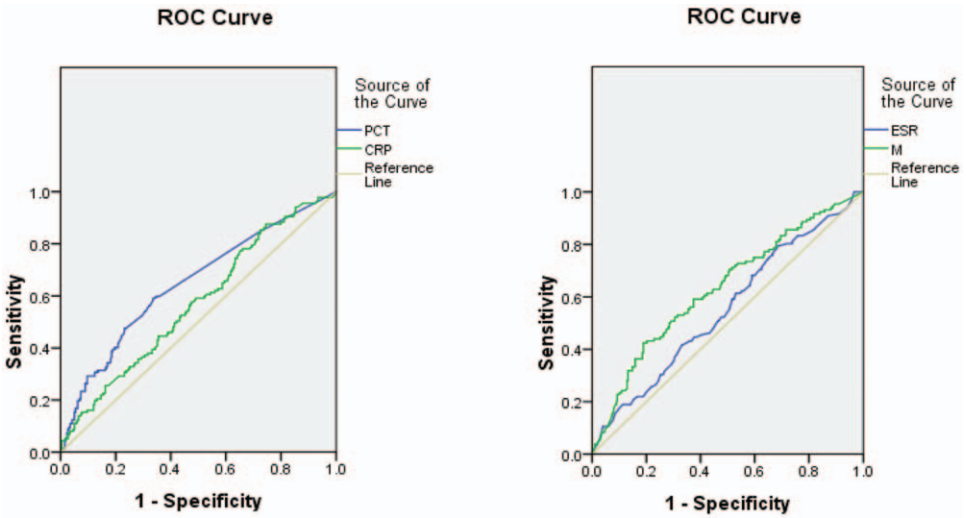

Figure 2. The ROC curve was made to study the sensitivity and specificity of the M value, PCT, CRP, and ESR to predict the severity of disease. APACHE II score ≥15 was divided into serious group, and APACHE II score <15 was divided into light-medium group. The AUC of M was 0.632 (95% CI 0.575–0.690, $P < .001$), PCT was 0.647 (95% CI 0.589–0.705, $P < .001$), CRP was 0.570 (95% CI 0.511–0.629, $P = .022$), and ESR was 0.553 (95% CI 0.494–0.612, $P = .078$). APACHE II = Acute Physiology and Chronic Health Evaluation II, CI = confidence interval, CRP = C-reaction protein, ESR = erythrocyte sedimentation rate, PCT = procalcitonin, ROC = receiver-operating characteristic.

Table 3

The relationship between APACHE II score and M value in various systemic diseases.

Patients with the primary admission diagnosis (n = 484)*							
Characteristics	**Respiratory system diseases (n = 376)**	**Digestive system diseases (n = 25)**	**Nerve system diseases (n = 11)**	**Urinary system diseases (n = 6)**	**AIDS (n = 13)**	**ICU severe infection (n = 22)**	**Other causes (n = 31)**
APACHE II	11.40 ± 6.06	8.64 ± 5.60*	19.18 ± 9.45	16.67 ± 6.31	10.62 ± 7.45	15.00 ± 9.38	8.23 ± 4.94*
M value	4.51 ± 3.15	2.20 ± 1.64*	2.13 ± 2.06	1.85 ± 2.12	2.40 ± 2.29	1.91 ± 1.88*	3.74 ± 2.23
Hospital mortality rate	2.66%	4.00%	0%	0%	0%	27.27%	0%

Primary admission diagnosis	**Partial regression coefficient *b***	**Standard error S_b**	**Standardized partial regression coefficient†**	***t***	***P***	**Collinearity statistics**	
						Tolerance	***VIF***
Constant	8.826	0.756		11.667	<.001	—	—
Respiratory system diseases	2.577	0.823	0.165	3.130	.002	0.695	1.439
Nerve system diseases	10.356	2.040	0.237	5.076	<.001	0.883	1.133
Urinary system diseases	7.841	2.675	0.133	2.931	.004	0.932	1.073
ICU severe infection	6.174	1.539	0.198	4.013	<.001	0.794	1.259
	$F = 9.965$		$P < .001$		$R^2 = 0.077$		

Primary admission diagnosis	**Partial regression coefficient *b***	**Standard error S_b**	**Standardized partial regression coefficient**	***t***	***P***	**Collinearity statistics**	
						Tolerance	***VIF***
Constant	2.581	0.284	—	9.100	<.001	—	—
Respiratory system diseases‡	1.933	0.322	0.264	6.006	<.001	1.000	1.000
	$F = 36.071$		$P < .001$		$R^2 = 0.070$		

AIDS = acquired immune deficiency syndrome.

ICU severe infection: bacteremia (1), septicemia (3), sepsis (8), septic shock (4), multiple organ failure (MOF) (5), cachexia (1).

* Compared with the respiratory system diseases, $P < .008$ was statistically significant different ($P < .008$, the test level needed to be adjusted for multiple pair-wise comparisons of data, inspection level α' = inspection level α/times of comparing).

† The standard partial coefficient predicted that neurological diseases had a greater impact on APACHE II scores.

‡ M values had a linear relationship with respiratory system diseases.

Table 4

The relationship between APACHE II and M value in respiratory system diseases.

Respiratory system diseases	**APACHE II (mean ± SD)**	**M value (mean ± SD)**	**Hospital mortality**
Severe pneumonia (n = 83)	13.78 ± 5.69*	2.91 ± 2.64*	8.43%
AECOPD (n = 133)	14.83 ± 4.15	4.85 ± 3.13*	0%
COPD (n = 5)	12.60 ± 2.97	7.10 ± 3.08	0%
Bacterial pneumonia (n = 82)	6.15 ± 4.04*	5.62 ± 3.22*	0%
Pulmonary abscess (n = 12)	11.50 ± 7.26	2.31 ± 2.82	8.33%
TB (n = 28)	4.89 ± 4.08*	4.69 ± 2.54*	0%
Lung CA (n = 15)	9.67 ± 4.10	3.68 ± 2.69	0%
Bronchiectasis with infection (n = 7)	9.14 ± 3.67	5.43 ± 2.14	0%
Pulmonary fibrosis (n = 3)	11.33 ± 5.03	4.92 ± 3.73	0%
Others (n = 8)	11.13 ± 8.59	5.84 ± 3.77	12.50%
Total χ^2	$\chi^2 = 163.240$, $P < .001$	$\chi^2 = 48.829$, $P < .001$	

APACHE II	**M value (mean ± SD)†**
0–4 (n = 54)	5.83 ± 2.68
5–9 (n = 90)	4.45 ± 3.38
10–14 (n = 108)	4.91 ± 3.04
15–19 (n = 95)	4.13 ± 3.08
20–24 (n = 21)	2.34 ± 2.37
25–29 (n = 6)	0.90 ± 1.17
30–34 (n = 2)	1.06 ± 0.52

M value	**APACHE II (mean ± SD)†**
0.00–2.99 (n = 143)	13.27 ± 6.47
3.00–5.99 (n = 108)	10.79 ± 5.56
6.00–9.99 (n = 91)	9.81 ± 5.44
≥10 (n = 34)	9.71 ± 5.45

AECOPD = acute exacerbation of chronic obstructive pulmonary disease, CA = cancer, COPD = chronic obstructive pulmonary disease, TB = tuberculosis.

* Compared with severe pneumonia, $P < .006$ was statistically significant different ($P < .006$, the test level needed to be adjusted for multiple pair-wise comparisons of data, inspection level α' = inspection level α/times of comparing).

† The correlation between APACHE II scores and M values in respiratory system diseases.

Table 5

The relationship between APACHE II and different respiratory system diseases.

Respiratory system diseases	Partial regression coefficient *b*	Standard error S_b	Standardized partial regression coefficient	*t*	*P*	Collinearity statistics	
						Tolerance	*VIF*
Constant	10.660	0.667	—	15.983	<.001	—	
Severe pneumonia	3.120	0.846	0.213	3.688	<.001	0.485	2.063
AECOPD	4.167	0.782	0.329	5.326	<.001	0.423	2.362
Bacterial pneumonia	−4.514	0.846	−0.308	−5.334	<.001	0485	2.063
TB	−5.767	1.113	−0.251	−5.181	<.001	0.693	1.444
	F=61.856		P<.001			R^2=0.401	

AECOPD = acute exacerbation of chronic obstructive pulmonary disease, APACHE II = Acute Physiology and Chronic Health Evaluation II, TB = tuberculosis.

4. Discussion

Lymphocytes are the key players of adaptive immune responses.[11–13] Apoptosis is a process of removing self-reactive lymphocytes. The imbalance of lymphocyte apoptosis in critically ill patients may lead to immunosuppression, making the patient prone to secondary infection or decreasing the ability to resist existing infection, leading to MOF.[14,15] From this perspective, some studies suggest that the disorder of lymphocyte apoptosis may reduce the ability of patients to respond to opportunistic infection.[16,17]

Human IFN-γ is produced by lymphocytes upon cellular activation by mitogens, antigens, or OKT3 monoclonal antibody.[18–20] The mitogen receptor of human T cells is PHA. PHA binds with T-cell receptors, and then T cells are activated mainly through phosphoinositol lipid metabolism. Potential biomarkers should ideally be easy to perform, be reproducible, and accurately predict outcomes such as severity of diseases or survival.[21,22] In this study, we prospectively evaluated IFN-γ release in response to PHA by using a QFT-GIT kit. It is a simple approach, but is standardized and useful. The results are valuable to guide clinical decisions.[23]

To our knowledge, this is the first study to show that M values can be used to predict the outcomes of diseases. The results of this study have revealed a direct significant inverse association between APACHE II scores and M values. When APACHE II scores were greater than 15 and M values were less than 6, the hospital mortality rose in a straight line.

Woo et al[24] previously showed that the lymphocyte count affects QFT-GIT results, and the neutrophil-to-lymphocyte ratio is an independent predictor of indeterminate QFT-GIT result. In our study, there was a positive correlation between M value and lymphocyte, whereas an inverse correlation between M values and WBC. Neurological diseases had a great influence on APACHE II scores, whereas respiratory diseases had a great influence on M values. M values may be a clinically useful immune biomarker, which may help clinicians objectively evaluate the severity of diseases especially in the respiratory system.

In older patients with infection, the initial CRP value alone did not have a prognostic value.[25] Importantly, discrepancies between ESR and CRP measurements have been commonly reported in chronic inflammatory diseases.[26] PCT had a diagnostic accuracy for bacteremia. In particular, low PCT levels could be used to rule out the presence of bacteremia.[27] In our study, the results showed the PCT and CRP are better than M values and ESR to predict the severity of diseases, but M values are more specific.

There were several limitations to this study. The overall size of the cohort was small and the results need further validation in a larger cohort. Because immune response defects were multifactorial, it was difficult to predict negative outcomes with only one parameter. In the next step, other cytokine measurements such as tumor necrosis factor-α, interleukin (IL)-1, IL-6, and IL-10 would be of interest to us, especially in sepsis.

5. Conclusions

In the early assessment, similar to APACHE II score, PCT and CRP have a better predictive value than M values and ESR. Both APACHE II scores and M values are ideal predictors of disease outcomes. The numbers and proportions of lymphocytes affect the results of M values. M values may be a clinically useful immune biomarker, which may help clinicians objectively evaluate the severity of diseases, especially in the respiratory system.

Table 6

The relationship between M value and different respiratory system diseases.

Respiratory system diseases	Partial regression coefficient *b*	Standard error S_b	Standardized partial regression coefficient	*t*	*P*	Collinearity statistics	
						Tolerance	*VIF*
Constant	5.466	0.258	—	21.153	<.001	—	—
Severe pneumonia	−2.554	0.417	−0.337	−6.128	<.001	0.790	1.266
AECOPD	−0.612	0.365	−0.093	−1.676	.095	0.774	1.293
Pulmonary abscess	−3.153	0.898	−0.176	−3.511	.001	0.947	1.055
Lung CA	−1.781	0.812	−0.111	−2.194	.029	0.936	1.068
	F=11.752		P<.001			R^2=0.112	

AECOPD = acute exacerbation of chronic obstructive pulmonary disease, CA = cancer.

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