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Original Article

Constructing a predictive model based on peripheral blood signs to differentiate infectious mononucleosis from chronic active EBV infection

Jin hua Yuan[1], Chong jie Pang[1], Shuang long Yuan[1]

[1] *Department of Infection Diseases, General Hospital of Tianjin Medical University, Tianjin, China*

Abstract

Objective: To develop a prediction model based on peripheral blood signs to distinguish between infectious mononucleosis and chronic active EBV infection.

Methods: Retrospective data was collected for 60 patients with IM (IM group) and 20 patients with CAEBV infection (CAEBV group) who were hospitalized and diagnosed at the General Hospital of Tianjin Medical University between December 2018 and September 2022. The analyses used were univariate and LASSO (least absolute shrinkage and selection operator) logistic regression.

Results: Univariate analyses revealed that both IM and CAEBV-infected patients displayed overlapping and intersecting clinical manifestations, such as fever, sore throat, enlarged lymph nodes, and enlargement of the liver and spleen, and that in contrast to inflammatory responses in peripheral blood, CAEBV-infected patients had more severe inflammatory responses. Nine biomarkers—HGB, lymphocyte count, percentage of lymphocytes, ALB, fibrinogen, CRP, IFN-, IL-6, and EBV-DNA load—were subsequently selected by LASSO logistic regression modeling to serve as discriminatory models.

Conclusions: Our investigation offers a solid foundation for diagnosing IM and CAEBV infection using the LASSO logistic regression model based on the significance and availability of peripheral blood indicators. Infected patients with CAEBV require early medical attention.

Key words: Chronic active Epstein-Barr virus; LASSO; logistic regression; differential diagnosis.

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Introduction

Most humans are vulnerable to the DNA double-stranded herpesvirus known as the Epstein-Barr virus (EBV), which is characterized by lymphocytophilia [1]. It often infects youth and causes little to no pain. Adults with primary infection can develop infectious mononucleosis (IM), characterized by an acute fever, hepatosplenomegaly, and enlarged lymph nodes [2]. However, a tiny minority acquire chronic active Epstein-Barr virus (CAEBV) infection, which typically happens in hosts that are only somewhat impaired and have recurrent IM-like symptoms such as fever, hepatosplenomegaly, and enlarged lymph nodes. Patients have significant and deadly comorbidities such as malignant lymphoma, hemophagocytic lymphoproliferative syndrome (HLH), multi-organ failure, and diffuse intravascular coagulation (DIC) throughout the disease [3,4]. The majority of CAEBV patients obtain appropriate and timely care with the use of clinical recommendations and multivariate mathematical models. However, the misdiagnosis rate remains high when IM and CAEBV are identified. It is challenging to anticipate the evolution of malignancy at an early stage due to the low prevalence of CAEBV in adults, its uncertain pathophysiology, and the complexity and heterogeneity of its clinical symptoms. These factors can also cause crossover and overlap with atypical and recurring IM cases. Clinicians urgently need to make accurate and prompt diagnoses and differential diagnoses at an early stage of the disease due to the variability of its clinical manifestations and its high mortality. There isn't any pertinent domestic or international research in this field at the moment. One of the popular machine learning algorithms in clinical practice, LASSO, is a reliable high-dimensional predictor regression method [5]. Clinical professionals can benefit from rigorous monitoring of peripheral blood biomarkers for early detection of IM and CAEBV infection, as well as prompt clinical intervention for CAEBV infection, with the use of highly accurate and practical predictive models.

Objects and methods

Clinical data

Clinical data were collected from 60 patients with IM and 20 patients with CAEBV infection who were

hospitalized in the General Hospital of Tianjin Medical University from December 2018 to September 2022. The Ethics Committee of Tianjin Medical University General Hospital gave its approval to the project.

The diagnostic criteria for IM and CAEBV were as follows:

IM: (1) Clinical manifestations of fever, pharyngitis, and lymph node enlargement in combination with any of sore throat, rash, hepatomegaly, splenomegaly, or liver function abnormalities; (2) peripheral blood lymphocytes (> 50%) and isotypic lymphocytes ≥ 10%; (3) positivity for EBV-VCA IgM antibodies or EBV-DNA; and (4) exclusion of purulent tonsillitis, other herpesvirus infections, hepatitis, HIV infection, leukaemia, and lymphoma [6,7].

CAEBV: WHO's updated version of the diagnostic criteria for CAEBV proposed by Okano *et al.* in Japan [8]: (1) prolonged or intermittent episodes of IM-like symptoms (fever, enlarged lymph nodes, and hepatosplenomegaly) lasting more than 3 months; (2) other systemic symptoms that have been seen in patients with IM, including haematological, gastrointestinal, neurological, pulmonary, ophthalmologic, dermatological, and cardiovascular complications; (3) an elevated EBV DNA load in peripheral blood or affected tissues (peripheral blood EBV-DNA > 102.5 copies/μg DNA is diagnostic) and the presence of EBV infection. (3) Elevated EBV-DNA load in peripheral blood or affected tissues (peripheral blood EBV-DNA greater than 102.5 copies/μg DNA has diagnostic significance) and the presence of EBV-infected T/NK cells; and (4) Exclusion of EBV primary infections, IM, and immune system diseases.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) patients aged ≥ 16 years, (2) diagnosed during hospitalization at our hospital, (3) fulfilled the diagnostic criteria for IM or CAEBV, (4) had complete clinical data, (5) even if the CAEBV infection was secondary to EBV-HLH, EBV-T/NK-cell lymphoma, or leukaemia, the diagnosis of the original CAEBV remained unchanged [8].

The exclusion criteria were as follows: (1) The patient had a combination of purulent tonsillitis, other herpes virus infections, hepatitis, HIV infection, and immune system disorders. (2) The patient has taken glucocorticoids or immunosuppressants within 3 months before hospitalization. (3) The patient has a combination of major diseases, such as mental disorders.

Research Methods

Clinical data, including age, gender, underlying diseases, and clinical manifestations, as well as peripheral blood indices were collected from the hospitalized patients in both groups and analyzed by univariate and LASSO-logistic regression analyses.

Table 1. Comparison of the basic information and clinical presentation of the two patient groups.

	IM (N = 60)	CAEBV (N = 20)	χ^2/Z	*p*
Age (years)	24.80 ± 8.3	40.85 ± 20.82	-3.361	< 0.010
Sex			1.351	0.245
Male	33 (55.0)	8 (40.0)		
Female	27 (45.0)	12 (60.0)		
Underlying Diseases				
Hypertension	2 (3.3)	1 (5.0)	0.000	1.000
Diabetes	2 (3.3)	0 (0.0)	0.000	1.000
Coronary artery disease	0 (0.0)	2 (10.0)	2.735	0.098
General Presentation				
Fever	54 (90.0)	20 (100.0)	0.961	0.327
Sore Throat	39 (65.0)	10 (50.0)	1.422	0.233
Bilateral eyelid edema	4 (6.7)	0 (0.0)	0.351	0.554
Rash	17 (28.3)	8 (40.0)	0.950	0.330
Hepatomegaly	20 (33.3)	9 (45.0)	0.883	0.347
Splenomegaly	50 (83.3)	15 (75.0)	0.684	0.408
lymphadenopathy	54 (90.0)	20 (100.0)	0.961	0.327
Jaundice	1 (1.7)	3 (15.0)	3.158	0.076
System symptoms	22 (36.7)	10 (50.0)	1.111	0.292
Complications				
HLH	0 (0.0)	12 (60.0)		< 0.001
Opportunistic infections	3 (5.0)	12 (60.0)	26.284	< 0.001
Multiple Organ Failure	0 (0.0)	4 (20.0)	8.772	< 0.010
Length of hospitalization(days)	10.0 [8.0-12.0]	27.0 [19.0-34.0]	-5.621	< 0.001

HLH (Hemophagocytic Lymphohistiocytosis), CAEBV (Chronic Active Epstein-Barr Virus), and System Symptoms (It generally involves the respiratory, circulatory, digestive, urinary, and nervous systems and includes clinical signs such as cough and sputum and dyspnea, headache and dizziness, nausea and vomiting, and elevated urine protein and cardiac enzymes).

Statistical analysis

SPSS Statistics 25.0 software was used to analyze the data, and count data conforming to normal distribution were described by frequency/percentage, and comparisons between the two groups were made using the chi-square test or the continuity modified chi-square test; measure data conforming to normal distribution were expressed as ($\bar{x} \pm S$), and comparisons between the two groups were made using the t-test for independent samples. Measures that did not conform to the normal distribution were described as median and interquartile spacing, and comparisons between the two groups were made using the Mann-Whitney U test. LASSO logistic regression models were used to determine the most valuable biological indicators for identifying IM and CAEBV, and LASSO logistic regression analyses were performed using R software (version 4.3.0) and the "glmnet" package (version 4.1-7). A $p < 0.05$ indicates a statistically significant difference.

Results

General information and clinical presentation

The ratio of men to women in the IM and CAEBV groups was 1:0.81 and 0.67:1, respectively. 4 patients in the IM group had comorbid underlying diseases (2 hypertensive disorders and 2 diabetes mellitus), and 3 patients in the CAEBV group had comorbid underlying diseases (1 diabetes mellitus and 2 coronary artery diseases). Between the two groups, there was a significant age difference ($p < 0.05$), with CAEBV infection being more common in young and middle-aged people and IM being more common in teenagers. Gender and co-occurring underlying disorders did not significantly differ ($p > 0.05$). Table 1 shows general clinical signs such as fever, sore throat, bilateral eyelid oedema, hepatomegaly, splenomegaly, lymph node enlargement, concomitant rashes, jaundice, and other systemic symptoms which were not significantly different between the two groups ($p > 0.05$). However, there were substantial differences between the two groups in terms of consequences such as HLH, opportunistic infections, and multiple organ failure ($p < 0.05$). Patients with CAEBV infection were more likely to experience multiple organ failure, opportunistic infections, and HLH problems than IM patients. Notably, there were no patients with concomitant HLH in the IM group, while 60% of patients in the CAEBV group had the condition. Between the IM and CAEBV groups, there was a statistically significant difference in the length of hospital stays, with CAEBV-infected patients needing a longer hospital stay ($p < 0.001$).

Peripheral blood bioindicators

Based on the importance and accessibility of biomarkers, a univariate analysis of peripheral blood biomarkers was conducted in two groups of patients, and the results provided influential factors that may identify IM and CAEBV infections, including WBC, HGB, lymphocyte count, percentage of neutrophils, percentage of lymphocytes, NLR, ALT, ALB, D-Dimer, fibrinogen, PCT, CRP, serum ferritin, IFN-γ,

Table 2. compares the peripheral blood biomarkers in the two patient groups.

	IM (N = 60)	CAEBV (N = 20)	t/Z/χ^2	*p*
WBC ($\times 10^9$/L)	10.5 ± 5.4	7.1 ± 6.9	2.285	< 0.010
HGB (g/L)	133.3 ± 19.1	105.3 ± 23.8	5.334	< 0.001
PLT ($\times 10^9$/L)	181.4 ± 58.3	162.3 ± 112.5	0.727	0.475
lymphocyte count ($\times 10^9$/L)	7.8 ± 10.8	1.5 ± 1.1	2.590	< 0.050
Percentage of neutrophils (%)	25.6 ± 15.9	57.0 ± 20.5	-7.121	< 0.001
Percentage of lymphocytes (%)	63.2 ± 16.0	32.4 ± 20.1	7.004	< 0.001
NLR	0.6 ± 0.8	4.2 ± 6.7	-2.416	< 0.050
Triglyceride (mmol/L)	1.8 ± 0.7	2.2 ± 1.8	-0.952	0.352
Cholesterol (mmol/L)	3.5 ± 0.7	3.8 ± 1.0	-1.136	0.266
ALT (U/L)	245.7 ± 203.1	111.0 ± 139.8	3.300	< 0.010
AST (U/L)	144.0 ± 114.0	117.0 ± 122.6	0.899	0.371
LDH (U/L)	468.7 ± 169.	530.9 ± 392.0	-0.683	0.502
ALB (g/L)	35.8 ± 3.8	30.4 ± 4.6	5.218	< 0.001
D-Dimer (ug/mL)	1.1 [0.8,1.6]	2.9 [1.0,7.9]	-2.950	< 0.010
Fibrinogen (g/L)	2.4 [1.9,2.8]	4.0 [3.0,4.6]	-4.428	< 0.001
PCT (ng/mL)	0.1 [0.1,0.2]	0.3 [0.1,2.6]	-3.559	< 0.001
CRP (mg/L)	5.5 [2.2,11.8]	36.3 [17.3,104.9]	-4.461	< 0.001
Serum ferritin (ug/mL)	0.7 [0.3,0.8]	3.1 [0.6,7.3]	-3.911	< 0.001
IFN-γ (pg/mL)	4.7 [2.9,6.1]	7.7 [3.4,10.1]	-2.689	< 0.010
TNF-α (pg/mL)	1.2 [0.3,2.7]	2.6 [0.7,4.1]	-1.813	0.070
IL-10 (pg/mL)	11.0 [6.3,12.3]	10.0 [2.9,13.3]	-0.456	0.648
IL-6 (pg/mL)	5.1 [2.9,10.0]	25.6 [13.3,45.4]	-5.208	< 0.001
EBV-DNA > 10^3 copies/mL	7 (11.7)	18 (90.0)	-39.273	< 0.001

WBC: white blood cell count; HGB: hemoglobin; PLT: platelet count; NLR: neutrophil-lymphocyte ratio; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALB: albumin; LDH: lactate dehydrogenase; PCT: procalcitonin; CRP: C-reactive protein; IFN: interferon; IL: interleukin).

IL-6, and EBV-DNA load and statistical comparison of these 16 peripheral blood biomarkers between the two patient groups ($p < 0.050$) are shown in Table 2.

LASSO logistic regression analysis

Variables were assigned to the potential influences in the univariate analysis, and the Variance Inflation Factor (VIF) was calculated to remove the multicollinearity issue. VIF1 was calculated by adding all the assigned variables together, suggesting potential multicollinearity between the percentage of neutrophils and the percentage of lymphocytes. We decided to eliminate the percentage of neutrophils since earlier research has shown that EBV is a lymphophile. We then calculated VIF2, which revealed that there was no significant multicollinearity in the variables following the exclusion of the percentage of neutrophils. Variable assignments and risk factors selected by the LASSO-logistic regression model are shown in Table 3 [9]. To filter the 15 variables that correlate to VIF2, we used LASSO logistic regression analysis and generalized cross-validation of the model. The results are shown in Figure 1. Analysis of LASSO logistic regression, nine discriminators were chosen via LASSO logistic regression analysis, including HGB, lymphocyte count, percentage of lymphocytes, ALB, fibrinogen, CRP, IFN-, IL-6, and EBV-DNA load.

Discussion

The clinical symptoms of IM and CAEBV are very similar. Following an EBV infection, IM is a benign condition that is likely to go away on its own, whereas CAEBV is a lethal and progressive condition. Therefore, a clear distinction between the two is

Figure 1. The LASSO logistic regression analysis.

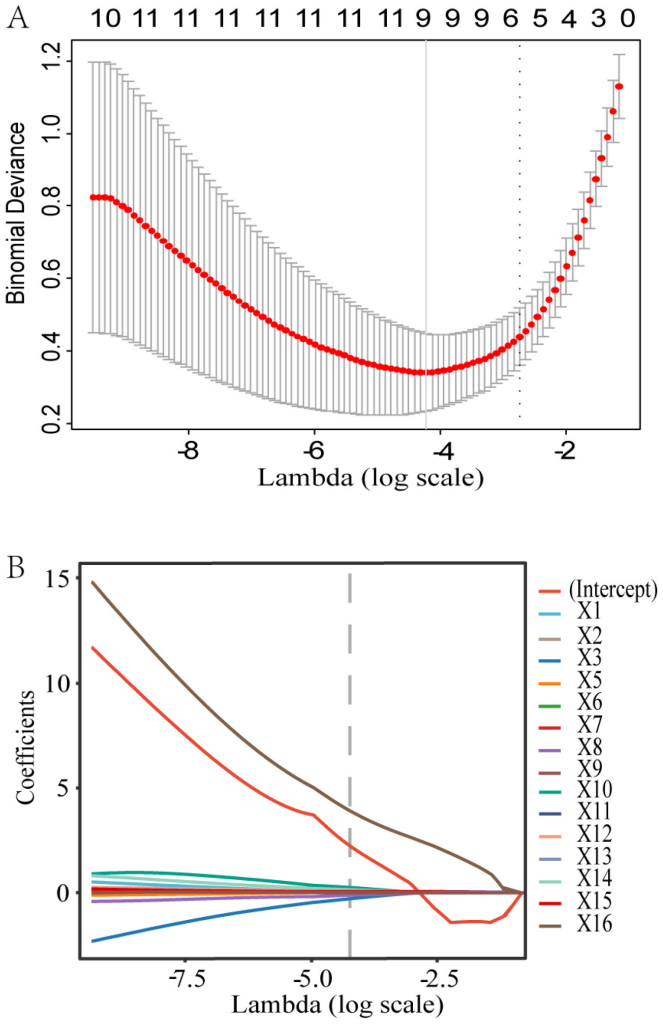

Table 3. Variable assignments and risk factors selected by LASSO-logistic regression model.

Variable	Risk Factors	Assignment	VIF1	VIF2	Coefficient
X1	WBC	continuous variable	3.052	3.047	
X2	HGB	continuous variable	2.540	2.522	-0.006
X3	lymphocyte count	continuous variable	3.514	3.510	-0.406
X4	Percentage of neutrophils	continuous variable	12.658		
X5	Percentage of lymphocytes	continuous variable	15.067	5.063	-0.020
X6	NLR	continuous variable	4.029	3.955	
X7	ALT	continuous variable	1.527	1.525	
X8	ALB	continuous variable	2.110	2.110	-0.181
X9	D-Dimer	continuous variable	1.764	1.727	
X10	Fibrinogen	continuous variable	2.323	2.285	0.272
X11	PCT	continuous variable	2.991	2.942	
X12	CRP	continuous variable	4.183	4.105	0.047
X13	Serum ferritin	continuous variable	2.132	2.108	
X14	IFN-γ	continuous variable	1.239	1.229	0.143
X15	IL-6	continuous variable	2.853	2.828	0.027
X16	EBV-DNA load	(> 1000 copies/mL = 1, < 1000 copies/mL = 0)	1.708	1.657	4.394

WBC: white blood cell count; HGB: hemoglobin; NLR: neutrophil-lymphocyte ratio; ALT: alanine aminotransferase; ALB: albumin; LDH: lactate dehydrogenase; IFN: interferon; IL: interleukin; PCT: procalcitonin; CRP: C-reactive protein). VIF1: Variance inflation factors calculated for all distributional variables. VIF 2: Variance inflation factor computed with GR% excluded. Coefficient: Regression coefficients calculated from LASSO logistic regression analysis after removing multicollinearity.

required, which is anticipated to enhance the current diagnostic techniques. In this work, the first differential prediction model was carried out along with the most extensive collection of peripheral blood biomarkers for both diseases. After completing univariate analyses, the results were strengthened by the use of LASSO logistic regression, and nine peripheral blood biomarkers turned out to be the most significant factors in distinguishing IM from CAEBV. The findings of this investigation demonstrated that CAEBV infection is more common in young and middle-aged adults than in teenagers with IM. After completing univariate analyses, the results were strengthened by the use of LASSO logistic regression, and nine peripheral blood biomarkers turned out to be the most significant factors in distinguishing IM from CAEBV. The findings of this investigation demonstrated that CAEBV infection is more common in young and middle-aged adults than in teenagers with IM. However, both groups experienced a fever, sore throat, bilateral oedema of the eyelids, hepatomegaly, splenomegaly, lymphadenopathy, and a combination of rash, jaundice, and other systemic symptoms during the disease's first course. Just as with HLH, opportunistic infections and multiple organ failure are more common in CAEBV infected individuals than in IM patients. This agrees with earlier studies reported in the literature [7,10].

The results of this study also showed that patients with IM and CAEBV infection had different peripheral blood biomarkers, with patients in the CAEBV group having lower WBC, HGB, lymphocyte count, lymphocyte ratio, ALT, and ALB than those in the IM group. The results of this study also showed that patients with IM and CAEBV infection had different peripheral blood biomarkers, with patients in the CAEBV group having lower WBC, HGB, lymphocyte count, lymphocyte ratio, ALT, and ALB than those in the IM group. Our results are consistent with those that have been published in the literature and appear to show that the inflammatory response is more severe and complex in patients with CAEBV infection than in those with IM [11]. In general, CAEBV and IM are inflammatory reactions to immunological dysregulation [12,13]. NLR can react to the severity or outcome of inflammatory and neoplastic disorders, according to earlier research [14,15]. Additionally, D-dimer and fibrinogen play a key role in the regulation of disease in the setting of inflammatory disorders and can trigger strong and harmful tissue inflammation. A wealth of literature has also shown that D-dimer can be used to forecast the development of EBV-related diseases [16-18]. It has been demonstrated that inflammatory cytokines, including IL-6 and IFN-γmay be produced by EBV-positive cells. IFN-γ can also be used to measure the extent of T-cell depletion in patients with EBV-positive NK-cell tumors, as elevated IFN- γcan react to the presence of a significant number of EBV-infected cells in the peripheral blood of these patients [19-21]. It is important to remember that EBV-DNA load is a direct and accurate measure of the level of viral replication activity in EBV-infected organisms [3]. In comparison to single and multifactor logistic regression analyses, the LASSO logistic regression model has much greater prediction accuracy and may incorporate numerous potential risk variables into a single instrument [22]. The most significant identifiers in this investigation were chosen with the aid of LASSO logistic regression analysis after the potential variables had been screened in the univariate analysis.

In conclusion, although IM and CAEBV share some clinical characteristics, they are entirely separate disease entities. While IM is a benign condition that usually resolves on its own, CAEBV is a fatal condition that progresses over time and is characterized by a strong storm of inflammatory agents, making early therapeutic intervention crucial [23]. This was the first time a novel method to distinguish between IM and CAEBV was proposed in this study. The implementation of the LASSO logistic regression model produced accurate data for the detection of IM and CAEBV infections based on the significance and accessibility of peripheral blood bioindicators. Additionally, it confirms that there needs to be more focus on the IM and CAEBV distinctions. This study's limitations include its retrospective nature and return bias. Future research will still require high-quality prospective studies.

Authors' contributions

Design of the study: Jinhua Yuan, Chongjie Pang, and Shuanglong Yuan; data collection: Jinhua Yuan, Chongjie Pang, and Shuanglong Yuan; interpretation and analysis of the data: Jinhua Yuan and Chongjie Pang; all authors reviewed the results and approved the final version of the manuscript.

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Corresponding author

Chongjie Pang
Department of Infection Diseases,
General Hospital of Tianjin Medical University,
Tianjin, China. 300052
Tel:15522501969
Email: echo0645@sina.com

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