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传染性单核细胞增多症患儿 NLR、CD4⁺/CD8⁺ 比值、ADA 与 EBV-DNA 载量的相关性分析及对肝损害的影响 *

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摘要 目的:探讨传染性单核细胞增多症(IM)患儿外周血中性粒细胞/淋巴细胞比值(NLR)、CD4⁺/CD8⁺ 比值、腺苷脱氨酶(ADA)与 EB 病毒(EBV)-脱氧核糖核酸(DNA)载量的相关性,分析其对 IM 患儿肝损害的影响。**方法:**选择 2019 年 1 月至 2022 年 4 月我院儿科收治的 102 例 IM 患儿(IM 组),另选择同期我科收治的 95 例 EB 病毒检测阴性的发热患儿(非 IM 组)和体检健康的 73 例健康儿童(对照组)。根据是否发生肝损害将 IM 患儿分为肝损害组(61 例)和非肝损害组(41 例)。比较外周血 NLR、CD4⁺/CD8⁺ 比值、ADA 与 EBV-DNA 载量, Pearson 法分析 NLR、CD4⁺/CD8⁺ 比值、ADA 与 EBV-DNA 载量的相关性。多因素 Logistic 回归分析 IM 患儿发生肝损害的影响因素。**结果:**IM 组 ADA 高于非 IM 组和对照组($P<0.05$),且非 IM 组高于对照组($P<0.05$),NLR、CD4⁺/CD8⁺ 比值低于非 IM 组和对照组($P<0.05$),且非 IM 组低于对照组($P<0.05$),IM 组 EBV-DNA 载量高于非 IM 组($P<0.05$)。IM 患儿 ADA 与 EBV-DNA 载量呈正相关($r=0.493, P<0.05$),NLR、CD4⁺/CD8⁺ 比值与 EBV-DNA 载量呈负相关($r=-0.419, -472, P<0.05$)。肝损害组 ADA、EBV-DNA 载量高于非肝损害组($P<0.05$),NLR、CD4⁺/CD8⁺ 比值低于非肝损害组($P<0.05$)。肝脏肿大、高 EBV-DNA 载量、高 ADA 是 IM 患儿肝损害的危险因素($P<0.05$),高 NLR、高 CD4⁺/CD8⁺ 比值是保护因素($P<0.05$)。**结论:**IM 患儿 ADA 增高, NLR、CD4⁺/CD8⁺ 比值降低,与 EBV-DNA 载量增加以及肝损害有关。

关键词:传染性单核细胞增多症; NLR; CD4⁺/CD8⁺ 比值; ADA; EBV-DNA; 相关性; 肝损害

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Correlation Analysis of NLR, CD4⁺/CD8⁺ Ratio, ADA and EBV-DNA Load in Children with Infectious Mononucleosis and Their Effects on Liver Damage*

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ABSTRACT Objective: To investigate the correlation between peripheral blood neutrophils/lymphocytes ratio (NLR), CD4⁺/CD8⁺ ratio, adenosine deaminase (ADA) and Ebarr Barr virus (EBV) -deoxyribonucleic acid (DNA) load in children with infectious mononucleosis (IM), and to analyze the influence on liver damage in children with IM. **Methods:** 102 children with IM (IM group) who were admitted to the Department of Pediatrics of our hospital from January 2019 to April 2022 were selected, as well as 95 children with fever with negative EB virus (non-IM group) who were admitted to our department during the same period and 73 healthy children (control group) in physical examination were selected. The children with IM were divided into liver damage group (61 cases) and non-liver damage group (41 cases) according to whether they had liver damage. Peripheral blood NLR, CD4⁺/CD8⁺ ratio, ADA and EBV-DNA load were compared. Pearson method was used to analyze the correlation between NLR, CD4⁺/CD8⁺ ratio, ADA and EBV-DNA load. Multivariate Logistic regression analysis was used to the influencing factors of the occurrence of liver damage in children with IM. **Results:** ADA in the IM group was higher than that in the non-IM group and control group ($P<0.05$), and the non-IM group was higher than the control group($P<0.05$), and the NLR and CD4⁺/CD8⁺ ratio were lower than those in the non-IM group and control group ($P<0.05$), and the non-IM group was lower than the control group ($P<0.05$), EBV-DNA load was higher in IM group than non IM group($P<0.05$). ADA was positively correlated with EBV-DNA load in the children with IM ($r=0.493, P<0.05$), while NLR and CD4⁺/CD8⁺ ratio were negatively correlated with EBV-DNA load ($r=-0.419, -472, P<0.05$). ADA and EBV-DNA load in the liver damage group were higher than those in the non-liver damage group ($P<0.05$), and NLR and CD4⁺/CD8⁺ ratio were lower than those in the non-liver damage group ($P<0.05$). Liver enlargement, high EBV-DNA load and high ADA were risk factors for liver damage in children with IM ($P<0.05$), and

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high NLR and high CD4⁺/CD8⁺ ratio were protective factors ($P<0.05$). **Conclusion:** The increase of ADA and the decrease of NLR and CD4⁺/CD8⁺ ratio in children with IM, and which are related to the increase of EBV-DNA load and liver damage.

Key words: Infectious mononucleosis; NLR; CD4⁺/CD8⁺ ratio; ADA; EBV-DNA; Correlation; Liver damage

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前言

传染性单核细胞增多症(IM)是一种主要由EB病毒(EBV)感染引起的单核-巨噬细胞系统急性增生性疾病,好发于4~6岁的儿童,临床表现为典型发热、咽炎、淋巴结肿大、肝脾肿大、外周血异型淋巴细胞增多等^[1,2]。肝损害是IM常见的并发症之一,以转氨酶水平升高为主要特征,EBV-脱氧核糖核酸(DNA)载量越高,肝损害的发生率越高,肝功能损伤程度越重^[3],严重者可出现重症肝炎或急性肝衰竭^[4,5]。探讨与肝损害相关标志物对指导临床治疗有着重要意义。中性粒细胞/淋巴细胞比值(NLR)是一种炎症和感染性指标,报道显示丙型肝炎病毒感染患者NLR显著增高^[6],且与肝功能衰竭和预后有关^[7]。CD4⁺/CD8⁺比值反映淋巴细胞免疫功能,CD4⁺/CD8⁺比值降低常见于免疫缺陷病毒感染、恶性肿瘤以及病毒感染^[8],CD4⁺/CD8⁺比值降低与丙型肝炎病毒感染患者肝硬化有关^[9]。腺苷脱氨酶(ADA)是一种嘌呤代谢酶,其突变可导致严重的免疫缺陷,与慢性乙型肝炎病毒(HBV)携带者疾病严重程度有关^[10]。本研究拟探讨IM患儿NLR、CD4⁺/CD8⁺比值、ADA与EBV-DNA载量的相关性以及肝损害的关系,以期临床肝损害预防和治疗提供参考。

1 资料与方法

1.1 一般资料

选择2019年1月至2022年4月我院儿科收治的102例IM患儿(IM组),男62例,女40例,年龄2~6岁,平均(4.00±1.02)岁。纳入标准:①至少具备发热、咽炎、颈淋巴结病、脾脏肿大、眼睑水肿、肝肿大以上三项临床症状,《诸福棠实用儿科学》中IM诊断标准^[11];②IgM抗EBV病毒衣壳抗原和IgG抗EBV衣壳抗原阳性,无EB核抗原抗体;③发病前14d内无慢性感染性疾病、免疫系统疾病史及使用免疫调节剂史;④患儿家属知情签署同意书。排除标准:①人类免疫缺陷病毒、巨细胞病毒、嗜肝病毒和单纯疱疹病毒等其它病毒感染或混合感染;②自身免疫性疾病;③既往肝、脾功能损伤儿童。肝损害诊断标准^[12]:丙氨酸氨基转移酶(ALT)>50 U/L为肝损害,根据是否并发肝损害将IM患儿分为肝损害组(61例)和非肝损害组(41例),另选择同期我科收治的95例EB病毒检测阴性的发热患儿(非IM组)和体检健康的73例健康儿童(对照组),非IM组患儿EBV特异性抗体阴性、聚合酶链反应(FQ-PCR)检测血浆EBV-DNA阴性,对照组均排除急性慢性感染、自身免疫性疾病以及肝脾肾功能损伤。非IM组,男58例,女37例,年龄2~7岁,平均(4.27±1.13)岁,对照组,男49例,女24例,年龄1~6岁,平均(4.05±1.06)岁,三组性别、年龄比较差异无统计学意义($P>0.05$),本研究已经获得我院伦理委员会批准。

1.2 NLR、CD4⁺/CD8⁺比值、ADA与EBV-DNA载量检测

所有受试儿入组当日采集空腹静脉血7 mL,2 mL注入EDTA抗凝试管混匀,采用UniCel DxH 600全自动血细胞分析仪(美国贝克曼库尔特公司)检测白细胞计数、异常淋巴细胞计数、中性粒细胞计数、淋巴细胞计数,计算NLR=中性粒细胞计数/淋巴细胞计数。3 mL注入干燥试管室温下静置,待血液凝固取上层液离心(相对离心力6 001×g,时间5 min)分离血清,采用LH750全自动生化分析仪(美国贝克曼库尔特公司)检测ADA、ALT、乳酸脱氢酶(LDH)、天冬氨酸氨基转移酶(AST)、总胆红素(TBiL)水平,ADA试剂盒购自武汉菲恩生物科技有限公司。2 mL注入肝素抗凝试管混匀,CD45-FITC/CD4-RD1/CD8-ECD/CD3-PC5(购自美国BD公司)混匀避光室温静置30 min,采用Attune NxT流式细胞分析仪(美国赛默飞公司)检测T淋巴细胞亚群CD4⁺占比、CD8⁺占比,计算CD4⁺/CD8⁺比值。EBV-DNA载量外送千麦医学检验实验室有限公司检测(对照组不检测该项目),LightCycler 480II荧光定量基因扩增分析仪(瑞士罗氏公司)采用实时荧光探针定量PCR技术检测EBV-DNA载量,EBV-DNA试剂盒购自湖南圣湘生物科技股份有限公司。

1.3 临床资料收集

收集患儿性别、年龄、热程、临床表现(颈部淋巴结肿大、咽扁扁桃体炎、肝脾肿大、脾脏肿大)、白细胞计数、异常淋巴细胞计数、中性粒细胞计数、淋巴细胞计数、NLR、ALT、LDH、AST、TBiL、ADA、CD4⁺占比、CD8⁺占比、CD4⁺/CD8⁺比值。

1.4 统计学方法

SPSS 25.00 进行数据分析,Kolmogorov-Smirnov法检验计量资料符合正态分布以($\bar{x} \pm s$)表示,多组间比较采用单因素方差分析(两两对比采用LSD-t检验)或独立样本t检验。计数资料以例(%)表示采用 χ^2 检验。Pearson分析NLR、CD4⁺/CD8⁺比值、ADA与EBV-DNA载量之间相关性,多因素Logistic回归分析IM患儿肝损害的影响因素。双侧检验水准 $\alpha=0.05$ 。

2 结果

2.1 IM组、非IM组、对照组NLR、CD4⁺/CD8⁺比值、ADA、EBV-DNA载量比较

IM组ADA高于非IM组和对照组($P<0.05$),NLR、CD4⁺/CD8⁺比值低于非IM组和对照组($P<0.05$),非IM组ADA高于对照组($P<0.05$),NLR、CD4⁺/CD8⁺比值低于对照组($P<0.05$),IM组EBV-DNA载量高于非IM组($P<0.05$),见表1。

2.2 NLR、CD4⁺/CD8⁺比值、ADA与EBV-DNA载量相关性

IM患儿ADA与EBV-DNA载量呈正相关($r=0.493, P<0.05$),NLR、CD4⁺/CD8⁺比值与EBV-DNA载量呈负相关($r=-0.419, -0.472, P<0.05$)。

2.3 肝损害组和非肝损害组NLR、CD4⁺/CD8⁺比值、ADA、EBV-DNA载量比较

肝损害组 ADA、EBV-DNA 载量高于非肝损害组($P<0.05$), NLR、CD4⁺/CD8⁺ 比值低于非肝损害组($P<0.05$),见表 2。

表 1 IM 组、非 IM 组、对照组 NLR、CD4⁺/CD8⁺ 比值、ADA、EBV-DNA 载量比较($\bar{x} \pm s$)

Table 1 Comparison of NLR, CD4⁺/CD8⁺ ratio, ADA and EBV-DNA load in the IM group, non-IM group and control group($\bar{x} \pm s$)

Groups	n	NLR	CD4 ⁺ /CD8 ⁺ ratio	ADA(U/L)	EBV-DNA load (logIU/mL)
IM group	102	0.89± 0.26 [°]	0.43± 0.16 [°]	34.60± 11.52 [°]	3.46± 1.27
Non-IM group	95	1.22± 0.32 [°]	0.54± 0.19 [°]	20.16± 5.12 [°]	1.05± 0.31
Control group	73	1.43± 0.20	0.66± 0.23	12.02± 2.03	-
F		86.691	30.866	191.983	18.003
P		0.000	0.000	0.000	0.000

Note: Compared with the control group [°] $P<0.05$, compared with the non-IM group [°] $P<0.05$.

表 2 肝损害组和非肝损害组 NLR、CD4⁺/CD8⁺ 比值、ADA、EBV-DNA 载量比较($\bar{x} \pm s$)

Table 2 Comparison of NLR, CD4⁺/CD8⁺ ratio, ADA and EBV-DNA load in the liver damage group and the non-liver damage group($\bar{x} \pm s$)

Groups	n	NLR	CD4 ⁺ /CD8 ⁺ ratio	ADA(U/L)	EBV-DNA load (logIU/mL)
Liver damage group	61	0.58± 0.17	0.35± 0.11	40.15± 9.47	4.21± 0.69
Non-liver damage group	41	1.35± 0.26	0.55± 0.16	26.35± 5.10	2.35± 0.51
t		18.099	7.486	8.528	14.754
P		0.000	0.000	0.000	0.000

2.4 IM 患儿肝损害的单因素分析

肝损害组肝脏肿大、淋巴细胞计数、异常淋巴细胞计数、ALT、AST、LDH、CD8⁺ 占比高于非肝损害组($P<0.05$),中性粒细胞计数、CD4⁺ 占比低于非肝损害组($P<0.05$),两组年龄、性

别、热程、颈部淋巴结肿大、咽扁桃体炎、脾脏肿大、白细胞计数、淋巴细胞计数、TBiL 比较差异无统计学意义($P>0.05$),见表 3。

表 3 IM 患儿肝损害的单因素分析

Table 3 Univariate analysis of liver damage in children with IM

Factors	Liver damage group (n=61)	Non-liver damage group(n=41)	t/χ^2	P
Age(years, $\bar{x} \pm s$)	4.06± 0.69	3.92± 0.52	1.105	0.272
Gender[n(%)]				
Male	39(69.93)	23(56.10)	0.632	0.427
Female	22(36.07)	18(43.90)		
Fever process(d)	6.02± 1.35	5.98± 1.57	0.137	0.891
Enlargement of cervical lymph nodes[n(%)]				
Yes	37(60.66)	23(56.10)	0.210	0.647
No	24(39.34)	18(43.90)		
Pharyngeal tonsillitis[n(%)]				
Yes	35(57.38)	21(51.22)	0.375	0.540
No	26(42.62)	20(48.78)		
Liver enlargement[n(%)]				
Yes	28(45.90)	9(21.95)	6.085	0.014
No	33(54.10)	32(78.05)		
Splenomegaly[n(%)]				
Yes	32(52.46)	15(36.59)	2.487	0.115
No	29(47.54)	26(63.41)		

White blood cell count($\times 10^9/L, \bar{x} \pm s$)	15.02 $\pm$ 2.35	14.78 $\pm$ 2.61	0.484	0.630
Neutrophil count($\times 10^9/L, \bar{x} \pm s$)	4.02 $\pm$ 1.80	8.12 $\pm$ 2.15	-10.424	0.000
Lymphocyte count($\times 10^9/L, \bar{x} \pm s$)	6.98 $\pm$ 1.54	6.03 $\pm$ 1.02	3.469	0.001
Abnormal lymphocyte count($\times 10^9/L, \bar{x} \pm s$)	11.32 $\pm$ 2.65	9.12 $\pm$ 2.48	4.217	0.000
ALT(U/L, $\bar{x} \pm s$)	57.26 $\pm$ 6.02	32.02 $\pm$ 5.35	21.693	0.000
AST(U/L, $\bar{x} \pm s$)	45.02 $\pm$ 3.59	30.44 $\pm$ 4.77	17.596	0.000
LDH(U/L, $\bar{x} \pm s$)	583.23 $\pm$ 106.95	501.24 $\pm$ 67.49	4.356	0.000
TBiL($\mu\text{mol/L}, \bar{x} \pm s$)	12.03 $\pm$ 3.26	11.75 $\pm$ 3.02	0.438	0.662
Proportion of CD4 ⁺ (%, $\bar{x} \pm s$)	20.35 $\pm$ 6.56	28.46 $\pm$ 9.56	-5.085	0.000
Proportion of CD8 ⁺ (%, $\bar{x} \pm s$)	58.12 $\pm$ 10.49	52.03 $\pm$ 7.14	3.244	0.002

2.5 IM 患儿肝损害的多因素 Logistic 回归分析

以 IM 患儿肝损害为因变量(赋值:0= 否,1= 是),肝脏肿大(赋值:0= 否,1= 是)、淋巴细胞计数、NLR、异常淋巴细胞计数、ALT、AST、LDH、ADA、CD8⁺ 占比、CD4⁺ 占比、CD4⁺/CD8⁺

比值、EBV-DNA 载量为自变量,原值输入,建立多因素 Logistic 回归方程,最终肝脏肿大、高 EBV-DNA 载量、高 ADA 是 IM 患儿肝损害的危险因素($P < 0.05$),高 NLR、CD4⁺/CD8⁺ 比值是保护因素($P < 0.05$),见表 4。

表 4 IM 患儿肝损害的 Logistic 回归方程

Table 4 Logistic regression equation of liver damage in children with IM

Variable	β	SE	Wald χ^2	OR(95%CI)	P
Constant term	9.065	3.182	8.116	-	0.000
Liver enlargement	1.352	0.415	10.613	3.865(1.714~8.718)	0.000
High EBV-DNA load	0.651	0.230	8.011	1.917(1.222~3.010)	0.000
High NLR	-0.712	0.207	11.830	0.491(0.327~0.736)	0.000
High ADA	0.531	0.196	7.340	1.701(1.158~2.497)	0.000
CD4 ⁺ /CD8 ⁺ ratio	-0.482	0.177	7.412	0.618(0.437~0.874)	0.000

3 讨论

IM 是原发性 EBV 感染的典型形式,EBV 是一种 γ -1 疱疹病毒,全世界约 95% 的成人感染过 EBV,通过唾液传播,儿童的潜伏期为 4 至 15 天,主要在 B 淋巴细胞中复制,也可在咽上皮细胞和腮腺导管中检出^[13]。EBV 感染 B 细胞,之后激活细胞毒性 T 细胞,引起非典型淋巴细胞增多,导致机体多个器官组织病理学改变,肝脏是 IM 常累及的器官之一,多表现为肝肿大和丙氨酸转氨酶水平升高,大多数 IM 肝损害由 EBV 激活的细胞免疫,异常增殖淋巴细胞、浆细胞和中性粒细胞浸润到中央静脉和肝小叶周围引起,EBV 感染后,脂质过氧化产生的自由基产生毒性作用,也可通过大量激活 B 淋巴细胞导致肝细胞损伤,引起淋巴结病和肝肿大^[14]。

NLR 是一种广泛使用、简单和可重复的炎症标记物,检测费用低,容易获得,常被临床用于诊断炎症或感染性疾病,现有报道显示新型冠状病毒感染肺炎患者入院时 NLR 显著升高,且与感染严重程度^[15]、严重急性呼吸衰竭以及不良预后有关^[16]。NLR 增高与肝功能损伤也存在密切关系,研究显示活体供肝移植后 NLR 偏高患者移植肝存活率较低,反之较高^[17]。本研究发现 IM 患儿 NLR 显著低于非 IM 患儿和对照组,NLR 与 EBV-DNA 载量呈负相关,肝损害组 NLR 低于非肝损害组,提

示 NLR 在 IM 患儿肝损害中异常表达,表明 NLR 可能作为 IM 的潜在标志物。分析原因为 NLR 反映中性粒细胞与淋巴细胞平衡状态,EBV 感染导致免疫系统激活,促使 T 淋巴细胞过度活化,大量淋巴细胞生成,引起淋巴细胞计数增加,并导致中性粒细胞破坏增加,因此 NLR 降低,大量异型淋巴细胞浸润于肝细胞,进而导致肝组织损伤。

CD4⁺/CD8⁺ 比值是一种免疫调节指标,正常值位于 1.4~2.0,CD4⁺/CD8⁺ 比值降低常见与病毒感染、肾病、癌症等免疫功能低下患者,CD4⁺/CD8⁺ 比值增高则多见于红斑狼疮、类风湿性关节炎等自身免疫性疾病患者^[18,19]。有研究发现,获得性免疫缺陷病毒感染儿童外周血 CD4⁺/CD8⁺ 比值降低,且与人免疫缺陷病毒载量有关^[20]。肝硬化小鼠模型 CD4⁺/CD8⁺ 比值降低,保肝药物治疗通过提高 CD4⁺/CD8⁺ 比值可减轻肝损伤,改善肝功能,逆转肝纤维化^[21]。本研究中 IM 患儿外周血 CD4⁺/CD8⁺ 比值显著降低,且与 EBV-DNA 载量、肝损害有关,低 CD4⁺/CD8⁺ 比值是 IM 患儿肝损害的危险因素,说明 CD4⁺/CD8⁺ 比值降低可能提示 IM 患儿具有更高的肝损害风险。IM 肝损害发病机制为 EBV 感染激活 CD8⁺T 细胞在肝脏中积累并产生干扰素- γ 、肿瘤坏死因子和 Fas 配体,介导肝细胞坏死和肝组织损伤^[14],低 CD4⁺/CD8⁺ 比值提示患儿 CD4⁺T 细胞减少,CD8⁺T 细胞增加,免疫功能降低,因此肝损害风险越大。

ADA 是一种免疫抑制信号 - 腺苷的降解酶, 在淋巴细胞和巨噬细胞的生长和分化、免疫稳态调节中发挥重要作用, 被认为是 T 淋巴细胞介导的细胞免疫的标记物^[22,23]。ADA 遗传缺陷可导致其底物腺苷和 2'-脱氧腺苷及其磷酸化衍生物浓度增加, 并导致细胞中 s-腺苷同型半胱氨酸水解酶的失活, 引起严重的免疫缺陷^[24,25]。在病毒感染疾病中血清 ADA 水平增高, 检测血清 ADA 水平有助于鉴别人免疫缺陷病毒单纯感染和合并肝炎病毒感染^[26], 血清 ADA 水平与人免疫缺陷病毒载量, CD8⁺ 细胞计数呈正相关, 与 CD4⁺ 细胞计数呈负相关^[27]。本研究发现 IM 患儿血清 ADA 水平显著增高, 且与 EBV-DNA 载量呈正相关, 是 IM 患儿肝损害的危险因素。分析原因为 EBV 感染后与免疫细胞的 EBV 受体结合, 引起 T 淋巴细胞活化、异常增殖、变形, 导致异型淋巴细胞占比增高, 异型淋巴细胞释放大量 ADA, 引起血清 ADA 水平增高^[28], EBV-DNA 载量越大, ADA 水平越高, 因此 ADA 可反映 IM 肝损害发生风险。

Logistic 回归分析显示 EBV-DNA 载量、肝脏肿大与 IM 患儿肝损害也有关, 肝脏肿大可能为 B 淋巴细胞激活后诱导肝脏炎症反应, 引起肝细胞水肿导致^[29], 而 EBV-DNA 载量越大, B 淋巴细胞活性增强越明显, 对肝脏造成的炎性损伤越大^[30]。

综上所述, IM 患儿的 ADA 水平、NLR、CD4⁺/CD8⁺ 比值异常, 且 ADA 与 EBV-DNA 载量呈正相关, NLR、CD4⁺/CD8⁺ 比值与 EBV-DNA 载量呈负相关, 肝脏肿大、高 EBV-DNA 载量、高 ADA 是 IM 患儿肝损害的危险因素, 高 NLR、CD4⁺/CD8⁺ 比值是保护因素。检测 NLR、ADA、CD4⁺/CD8⁺ 比值可辅助评估 IM 患儿肝损害风险。

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