The prognostic value of NLR for early death in secondary Hemophagocytic lymphohistiocytosis patients: an analysis of 92 patients

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Research

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Abstract

Background: Hemophagocytic lymphohistiocytosis (HLH) a hyperinflammation disease and have high early mortality. The neutrophil-lymphocyte ratio (NLR) plays a prognostic role in various inflammation conditions. However, the role of NLR in HLH remains unknown.

Results: 92 patients were collected from Sep 2014 to Dec 2019, the median age was 50 years (16-88) and 54 patients (58.6%) were male. 39 patients (42.3%) died during a 30-day follow-up. In addition, NLR was higher in nonsurvivor than survivor ($P=0.005$), higher NLR was correlated with older age ($P=0.020$), worse survival status ($P=0.006$), lower HB level ($P=0.008$), longer PT level ($P=0.010$), higher creatinine level ($P=0.027$) and higher IL-6 level ($P=0.008$) and in multivariate analysis, NLR ($HR=2.508$, $95\%CI: 1.275-4.934$), was indicated as an independent prognostic factor for early death.

Conclusions: NLR was correlated with early death in HLH, suggest NLR could be used as a reference indicator for the monitoring and management of HLH.

Background

Hemophagocytic lymphohistiocytosis (HLH) is a rare but life-threatening syndrome. HLH is characterized by an uncontrolled immune response and persistent activation of cytotoxic T lymphocytes and natural killer cells, subsequently excessed secretion of inflammatory cytokines and macrophage activation, leads to cytokines release storm, systemic inflammation and multiple organ failure[1, 2]. The following manifestations are usually observed in patients with HLH: fever, enlargement of the liver and the spleen, cytopenias, liver dysfunction, increased triglycerides and ferritin and hemophagocytosis in bone marrow, the liver, the spleen or the lymph nodes.[1-3]

HLH can be observed in all ages and categorized into primary HLH and secondary HLH according to the underlying triggering condition. Primary HLH is a familial inherit disease with an autosomal recessive form; secondary HLH often caused by infections, malignancy, and autoimmune/autoinflammatory disease [4, 5]. The clinical application of HLH-94 and HLH-2004 protocol decreased the overall mortality of primary HLH[6, 7], however, the specific treatment for secondary HLH is limited, and the early mortality remains high[8], it is urgent to stratifying high-risk patients, and initiate appropriate therapy in these patients[3, 9]. Therefore, a usefulness indicator of early death is needed.

Recently, a simple, rapid, inexpensive marker, the neutrophil-lymphocyte ratio (NLR) was suggested to be a robust biomarker of systemic inflammation and predicts early death and overall survival in various inflammation associated pathological conditions[10-13]. It is well known that increased neutrophil counts represent systemic inflammation and decreased lymphocyte counts represent the immune system[10], the combination of neutrophil and lymphocyte makes NLR as a more comprehensive biomarker. However, the prognostic value of NLR in HLH, a hyper-inflammation disease, remains unknown. In this study, we retrospectively analyzed a cohort of 92 patients with secondary HLH and analysis the associated of NLR and HLH 30-day mortality.

Results

Characteristics of patients

A total of 92 patients were included in our analysis, the median age at diagnosis of them was 50 years, ranged from 16-88, and 54 patients (58.6%) were male.

Regarding the triggering condition, 48 patients (52.2%) secondary to malignancy, 27 patients (29.3%) secondary to infections, 10 patients (10.9%) secondary to autoimmune disorders, and the underlying triggering disease of 7 patients (7.6%) were unknown. In addition, we analyzed the triggering condition according to age and gender, malignancy was the mainly triggering condition in all subgroup, the distribution was shown in Figure 1.

51 patients (55.4%) received only glucocorticoid therapy, 32 patients (34.8%) received glucocorticoid combined with etoposide, and 9 patients (9.8%) did not receive any special treatment for hemophagocytic syndrome and were only treated with supportive symptomatic treatment.

Patients Characteristics according to survival status and NLR

After diagnosis and initial treatment, all patients were followed up for at least 30 days. In our cohort, 39 patients died with a mortality of 42.3% after 30 days of observation. Patients were divided into two groups according to survival status, and the patient's characters, complete blood counts, NLR, biochemical indicators, and underlying triggering condition were compared. There was significant difference in age, lymphocyte counts, NLR, PLT, PT, APTT, FIB, Albumin, Creatinine, LDH, and splenomegaly (Table 1). Nonsurvivor were associated with elder ($P=0.04$), lower lymphocyte counts ($P=0.001$), lower PLT counts ($P=0.019$), lower FIB level ($P=0.024$), lower albumin level ($P=0.008$), higher NLR (0.005), longer PT level ($P=0.005$), longer APTT level (0.002), higher creatinine level ($P=0.017$), higher LDH level ($P=0.035$) and splenomegaly ($P=0.02$), respectively.

Furthermore, patients were also divided into two groups according to NLR median value, and higher NLR was correlated with older age ($P=0.020$), worse survival status ($P=0.006$), lower HB level ($P=0.008$), longer PT level ($P=0.010$), higher creatinine level (0.027) and higher IL-6 level ($P=0.008$) (Table 1), in addition, NLR were correlated with the length of survival (spearman correlation=-0.252, $P=0.016$).

Univariate analysis for 30-day-mortality

To further identify the potential indicators, cox regression was employed to identify the potential prognosis factors for 30-day-mortality. As shown in Table 2, $L \geq 0.62 \times 10^9/L$ (HR=0.427, 95%CI:0.219-0.833), $NLR \geq 2.99$ (HR:2.396, 95%CI:1.230-4.669), $PT \geq 13.3s$ (HR:2.620, 95%CI:1.303-5.269), $APTT \geq 39.5s$ (HR:2.701, 95%CI:1.366-5.340) and $albumin \geq 26 g/L$ (HR:0.346, 95%CI: 0.175-0.685) could be used as prognostic factors for 30-day-mortality.

Multivariate analysis for 30-day-mortality

In multivariate analysis, $NLR \geq 2.99$ (HR=2.508, 95%CI: 1.275-4.934) and $APTT \geq 39.5s$ (HR=2.780, 95%CI: 1.395-5.542) were associated with a poorer prognosis, $albumin \geq 26g/L$ (HR=0.384, 95%CI: 0.192-0.768) was associated with a better prognosis, and could be used as independent predictors for 30-day-mortality (Table 3). In addition, the Kaplan-Meier curve according to NLR, APTT, and albumin were shown in figure 2.

Discussion

In this study, we analyzed the potential prognostic value of NLR for 30-day mortality in a cohort of 92 patients with secondary HLH, and found that NLR was higher in nonsurvivor patients, in addition, a higher NLR was associated with increased 30-day mortality, and multivariate analysis indicates NLR was an independent predictor of 30-day mortality. To our best knowledge, this is the first study that investigates the relationship between NLR and the early death of HLH.

Based on the evidence published to date, secondary HLH was mainly secondary to malignancies and infections, and male patients had a higher incidence compared with female patients. Due to the rapidly progressing and limited specific treatment, secondary HLH had high early mortality, which ranged from 20.4% to 43.4%[4, 14-16], our result was consisted with it. Given this, it is necessary to carry out a usefulness indicator to stratifying patients.

In recent years, NLR as an inflammation indicator has been well studied in various inflammation associated pathological conditions[10-13]. Higher NLR was correlated with more advanced disease stage in autoimmune disease[17, 18] and it was proved to be an independent prognosis factor in infections disease[11, 19], diffuse large B-cell lymphoma[20, 21], and so on. Whilst, a higher NLR predicts increased 30-day mortality in critically ill patients[13, 22, 23]. In this study, we observed that nonsurvivor had a higher NLR compared with survivor, and higher NLR was correlated with older age, longer PT, higher creatinine, and lower HB. In addition, the univariate analysis identified the prognostic value of NLR, and multivariate analysis proved NLR was an independent prognosis factor for 30-day mortality. Above all, NLR is a reliable indicator to predict the early death in HLH.

The mechanism underlying the association of higher NLR and increased mortality in HLH patients remains unknown, we hypothesis that, on the one hand, the correlation between NLR and proinflammatory cytokines endowed the prognostic value of NLR. In HLH, excessive secretion of cytokines leads to local and systematic inflammation, tissues damage and organs failure, and higher measured cytokine levels was correlated with poorer outcomes[1, 24]. Published data indicated that NLR has a positive correlation with proinflammatory cytokines, such as interleukins (IL-1ra, IL-6, IL-7, IL-8, IL-9, IL-12), interferon γ and macrophage inflammatory protein 1 β [10]. And in our study, a positive correlation between NLR and IL-6 was also observed. On the other hand, the prognostic value of NLR may result from the relationship between NLR and dysregulated immune response (decreased NK cell activity and increased CD8+ T cell). Evidence indicated that NLR has a negative association with NK cell activity in healthy donor[25], otherwise, Yang *et al.*[26] assume that inflammatory response contributed to NK cell anergy, and NK cell anergy was associated with higher NLR in pancreatic cancer; Kang *et al.*[27] also found a negative correlation between NK cell activity and NLR in gastric cancer, breast cancer, and pancreatic cancer. In addition, a negative correlation between CD8+ T cell and NLR was observed in intrahepatic cholangiocarcinoma[28], it is notable that increased CD8+ T cell was favorably associated with survival in HLH[29]. Taken together, it is reasonable to accept the prognostic value role of NLR in HLH.

However, the present study also has several limitations that need to be acknowledged. First, the study was uncontrolled and retrospective in nature. Second, as a single-center analysis, we did not use ROC to determine

the cutoff value of NLR for the prediction of mortality. Finally, HLH is a systematic syndrome, a single indicator may have a bias to evaluate prognosis. Future multicenter and prospective studies are required to overcome these limitations, and a prognostic scoring system is needed, our study may shed some light on it.

In conclusion, our current study emphasizes the potential role of NLR as prognostic factors for early death in HLH, suggests NLR could be used as a reference indicator for the monitoring and management of HLH.

Patients And Methods

Patients

The study collected a total of 92 patients from Sep 2014 to Dec 2019, in the hematology department, the Second Hospital of Anhui Medical University, and carried out according to the approval of the institutional review board and informed consent before patient enrollment. The clinical diagnosis was made according to the 2004 Histiocyte Society Criteria for HLH diagnosis (HLH-2004)[7]: (1) fever ($\geq 38.5^{\circ}\text{C}$ for ≥ 7 days); (2) splenomegaly; (3) cytopenias affecting at least two of three lineages (i.e., hemoglobin (HB) $< 90\text{g/L}$, platelet count (PLT) $< 100 \times 10^9/\text{L}$, neutrophil count $< 1.0 \times 10^9/\text{L}$); (4) hypertriglyceridemia ($\geq 3\text{ mmol/L}$) and/or hypofibrinogenemia ($\leq 1.5\text{ g/L}$); (5) hemophagocytosis in bone marrow, spleen, liver, or lymphnodes; (6) hyperferritinemia ($\geq 500\text{ }\mu\text{g/L}$); (7) low or absent NK-cell activity; and (8) elevated level of serum soluble CD25 (i.e., soluble interleukin (IL)-2 receptor $\geq 2400\text{ IU/mL}$). It is unavailable to finish the test for soluble CD25 levels and NK cell activity, so the diagnosis was made when the patient meets the five of six criteria.

The clinical data and the following laboratory data were collected at the time of the diagnosis: complete blood count (WBC, neutrophil, lymphocyte, HB, PLT), coagulation function (prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen (FIB), D-Dimer), biochemical index (total bilirubin (TB), Triglyceride (TG), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AKP), Serum Ferritin (SF), Glutamyltranspeptidase (Y-GT), Albumin (ALB), Creatinine (CR), lactate dehydrogenase (LDH) and C-reactive protein (CRP)).

Statistical analysis

The continuous variates are presents as median (min-max), Categorical variates are presents as frequencies (percentages). Student's T test and Mann–Whitney U test were used for continuous variates comparison when appropriate, and the Chisquare test was used for categorical variates. Univariate and multivariate analyses were performed with Cox regression. All variables with a P value less than 0.1 in the univariate analyses were included in multivariate analysis with a stepwise method to determine independent prognosis factors. Kaplan-Meier method was used for the survival curve.

All P values were two sided, and P values < 0.05 was determined to be statistically significant. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS version 19.0, USA).

Abbreviations

HLH: Hemophagocytic lymphohistiocytosis

NLR: Neutrophil-lymphocyte ratio

PLT: Platelet

HB: Hemoglobin

PT: Prothrombin time

IL: Interleukin

APTT: Activated partial thromboplastin time

FIB: Fibrinogen

TB: Total bilirubin,

TG: Triglyceride

AST: Aspartate aminotransferase

ALT: Alanine aminotransferase

AKP: Alkaline phosphatase

Y-GT: Glutamyltranspeptidase

SF: Serum Ferritin

ALB: Albumin

CR: Creatinine

LDH: Lactate dehydrogenase

CRP: C-reactive protein

Declarations

Ethics approval and consent to participate

All procedures were performed in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

Consent for publication

Written informed consent was obtained from the parents of all subjects included in the study.

Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

All authors declare that they have no conflict of interest.

Conflicts of interest:

The authors declare that there is no conflict of interests regarding the publication of this paper

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Author contribution

LHH, FW and YP assisted the patient, performed data collection, analyzed the data, wrote the manuscript and approved the final manuscript as submitted. CW, JKZ, QL wrote the manuscript. WWZ, CD, YM, HPW, SDX and ZMZ assisted the patient.

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Tables

Table 1. Clinical and laboratory parameters of patients according to survival status.

	All patients	Survivor n=53	Nonsurvivor (n=39)	P value	NLR<2.99 (n=46)	NLR≥2.99 (n=46)	P value
Age (year)	50(16-88)	47(16-73)	58(19-88)	0.040*	46(16-88)	55.5(22-77)	0.020*
Sex-male	54(58.6%)	27 (50.9%)	27(69.2%)	0.078	26(56.5%)	28(60.9%)	0.672
Survivor	53	-	-	-	33(71.7%)	20(43.5%)	0.006*
WBC (109/L)	2.81(0.34-43.86)	2.88(0.36-43.86)	2.30(0.34-15.30)	0.288	-	-	-
N (109/L)	1.48(0.05-14.59)	1.38(0.1-11.83)	1.57(0.05-14.59)	0.847	-	-	-
L (109/L)	0.62(0.02-18.98)	0.84(0.1-18.98)	0.41(0.02-1.84)	0.001*	-	-	-
NLR	2.99(0.04-41.28)	2.04(0.04-25.24)	4.38(0.18-41.28)	0.005*	-	-	-
HB (g/L)	83(23-141)	81(43-141)	85(23-130)	0.853	74.5(43-130)	89(23-141)	0.008
PLT (109/L)	43.5(3-687)	45(8-687)	38(3-99)	0.019*	37.5(3-150)	48.5(15-281)	0.085
TB (μmol/L)	20.7(2.1-233.2)	20.4(2.1-106.6)	24.1(3.3-233.2)	0.136	22.5(2.1-233.2)	20.6(5.7-139.3)	0.800
TG (mmol/L)	2.45(0.61-65.30)	2.48(0.61-65.30)	2.35(0.75-11.46)	0.890	2.31(0.61-31.10)	2.71(0.75-65.30)	0.725
PT (s)	13.3(9.9-29.5)	12.9(9.9-18.0)	15.0(10.4-29.5)	0.005*	12.9(9.9-17.9)	14.1(11.6-29.5))	0.010
APTT (s)	39.5(21-177)	35.3(21-64)	46.4(21-177)	0.002*	39.5(21-75)	40.4(21-177)	0.355
FIB (g/L)	1.53(0.33-7.19)	1.65(0.34-7.19)	1.30(0.33-6.16)	0.024*	1.58(0.50-6.96)	1.43(0.33-7.19)	0.755
D-D	4.5(0.47-80.00)	4.51(0.55-80.00)	4.10(0.47-35.00)	0.873	3.49(0.55-40.00)	5.82(0.47-80.00)	0.171
ALT (U/L)	70.5(8-4310)	70(8-687)	77(15-4310)	0.684	73.5(15-687)	68.5(8-4310)	0.470
AST (U/L)	109.5(3-5579)	103(3-1104)	131(28-5579)	0.180	119(3-1356)	103.5(14-5579)	0.910
AKP (U/L)	141(34-2582)	120(34-1799)	162.5(38-2582)	0.174	143(34-1799)	131.5(38-2582)	0.562
Y-GT	98(7-700)	85.5(7-700)	130(12-631)	0.440	88.5(7-700)	101(10-698)	0.767
SF (ng/ml)	4595(171-	4590(175-	7180(171-	0.627	4495(171-	7350(749-	0.229

	212133)	212133)	117000)		138000)	212133	
ALB (g/L)	26(13-41.6)	27.3(15-37.6)	23.6(13.0-41.6)	0.008*	26.7(16.2-35.5)	24.4(13.0-41.6)	0.094
CR (mol/l)	69(28-1044)	67(32-1044)	81(28-407)	0.017*	66(34-267)	78.5(28-1044)	0.027*
LDH (U/L)	781.5(100-10873)	627(100-6480)	1053(196-10873)	0.035*	648(100-3187)	841.5(196-10873)	0.639
CRP (mg/L)	37.8(0.5-244.7)	37.3(0.5-244.7)	38.3(0.9-123.6)	0.874	29.1(0.50-183.26)	51.9(2.5-244.7)	0.016*
IL-6	40.0(1.6-5000.0)	39.0(1.6-1753.0)	43.5(4.0-5000.0)	0.721	27.0(3.9-1753.0)	61.2(1.6-5000.0)	0.008*
splenomegaly	66	43 [81.1%]	23[59.0%]	0.020*	37[80.4%]	29(63.0%)	0.064
hepatomegaly	22	14 [26.4%]	8[20.5%]	0.512	14(30.4%)	7(15.2%)	0.092
enlarged lymph nodes	41	23 [43.4%]	18[46.2%]	0.793	21(45.7%)	20(43.5%)	0.834
Triggering condition				0.096			0.135
malignancy	48	28	20		24	24	
Infections	27	17	10		17	10	
Autoimmune disorders	10	7	3		2	8	
Unknow	7	1	6		3	4	

*represent P<0.05

Table 2. Univariate Cox regression analysis

Factors	HR	95%CI	P
age≥50 (year)	1.627	0.859-3.083	0.135
Sex (male)	1.740	0.881-3.435	0.111
WBC≥2.81 (109/L)	0.983	0.542-1.842	0.957
N≥1.48(109/L)	1.100	0.587-2.062	0.765
L≥0.62 (109/L)	0.427	0.219-0.833	0.012*
NLR≥2.99	2.396	1.230-4.669	0.010*
HB≥83(g/L)	1.201	0.640-2.255	0.568
PLT≥43 (109/L)	0.212	0.355-1.259	0.212
PT≥13.3 (s)	2.620	1.303-5.269	0.007*
APTT≥39.5 (s)	2.701	1.366-5.340	0.004*
FIB≥1.53 (g/L)	0.620	0.328-1.175	0.143
ALB ≥26 (g/L)	0.346	0.175-0.685	0.002*
CR ≥69 (mol/l)	1.718	0.901-3.278	0.100
LDH ≥781 (U/l)	1.791	0.945-3.392	0.074
AST≥109.5(U/L)	1.200	0.639-2.252	0.571
ALT≥70.5(U/L)	1.093	0.583-2.047	0.782
AKP≥141(U/L)	1.258	0.670-2.361	0.476
Y-GT≥98	1.195	0.636-2.245	0.579
TB≥20.7(μmol/L)	1.338	0.712-2.512	0.365
TG≥2.45(mmol/L)	1.951	0.508-1.783	0.876
CRP≥37.8 (mg/L)	1.020	0.544-1.911	0.952
IL-6≥40.0	1.032	0.551-1.933	0.922
Etoposide	0.771	0.390-1.523	0.454

*represent P<0.05

Table 3. Multivariate Cox regression analysis

Factors	HR	95%CI	P
NLR $\geq$ 2.99	2.508	1.275-4.934	0.008*
APTT $\geq$ 39.5(s)	2.780	1.395-5.542	0.004*
Albumin $\geq$ 26 (g/L)	0.384	0.192-0.768	0.008*

*represent $P < 0.05$

Figures

Figure 1

Main triggering condition distribution in all patients, and distribution according to gender and age.

Figure 2

Kaplan-Meier curve according to NLR (A), Albumin (B) and APTT (C).