ANESTHESIA & PAIN MEDICINE

Anesth Pain Med 2023;18:389-396
https://doi.org/10.17085/apm.23048
pISSN 1975-5171 • eISSN 2383-7977

Original Article

Neutrophilia is more predictive than increased white blood cell counts for short-term mortality after liver transplantation in patients with acute-on-chronic liver failure

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Received April 17, 2023
Revised July 22, 2023
Accepted July 26, 2023

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Background: Acute-on-chronic liver failure (ACLF) is a life-threatening disease that requires urgent liver transplantation (LT). Accurate identification of high-risk patients is essential for predicting post-LT survival. The chronic liver failure consortium ACLF score is a widely accepted risk-stratification score that includes total white blood cell (WBC) counts as a component. This study aimed to evaluate the predictive value of total and differential WBC counts for short-term mortality following LT in patients with ACLF.

Methods: A total of 685 patients with ACLF who underwent LT between January 2008 and February 2019 were analyzed. Total and differential WBC counts were examined as a function of the model for end-stage liver disease for sodium (MELD-Na) score. The association between total and differential WBC counts and 90-day post-LT mortality was assessed using multivariable Cox proportional hazards regression analysis.

Results: The total WBC counts and neutrophil ratio were higher in patients with ACLF than in those without ACLF. The neutrophil ratio was significantly associated with 90-day post-LT mortality after adjustment (hazard ratio [HR], 1.04; P = 0.001), whereas total WBC counts were not significantly associated with 90-day post-LT mortality in either univariate or multivariate Cox analyses. The neutrophil ratio demonstrated a relatively linear trend with an increasing MELD-Na score and HR for 90-day post-LT mortality, whereas the total WBC counts exhibited a plateaued pattern.

Conclusions: Neutrophilia, rather than total WBC counts, is a better prognostic indicator for short-term post-LT mortality in patients with ACLF.

Keywords: Acute-on-chronic liver failure; Neutrophils; Leukocytosis; Liver transplantation.

KSTA

INTRODUCTION

Acute-on-chronic liver failure (ACLF) is a life-threatening disease for which liver transplantation (LT) is the only definitive treatment [1,2]. Therefore, accurately identifying patients at the highest risk of mortality is essential for not only optimizing the allocation of donor organs but also predicting post-LT survival [3]. The chronic liver failure consortium

(CLIF-C) ACLF score is a generally accepted risk-stratification parameter for predicting mortality in patients with ACLF. This score includes the total white blood cell (WBC) counts because leukocytosis has been established as a major determinant of waitlist mortality [1].

ACLF is characterized by overwhelming systemic inflammation and susceptibility to infection [4]. Neutrophils, the most abundant type of WBCs, play a vital role in the immune response and have been implicated in various inflammatory and pathological processes. Hence, understanding the prognostic value of neutrophilia in comparison to leukocytosis may provide insights for refining risk stratification and optimizing patient selection for LT.

This study aimed to evaluate the predictive value of the total and differential (neutrophils, lymphocytes, monocytes, basophils, and eosinophils) WBC counts for short-term mortality following LT in patients with ACLF. Identifying the superior prognostic indicator will aid clinicians in making informed decisions regarding patient prioritization and ultimately enhance outcomes for those undergoing LT.

MATERIALS AND METHODS

Patient selection

Data from prospectively registered patients who underwent LT from January 2008 to February 2019 were collected. The Institutional Review Board of Asan Medical Center approved this study and waived the requirement of obtaining informed consent (2023-0448). Of the total 4,205 LT recipients, 1,268 were excluded because 83 had pre-existing chronic end-stage renal disease and were receiving renal replacement therapy, 256 had acute toxic or fulminant hepatitis, 180 underwent re-transplantation, and 749 had incomplete data. Among the remaining 2,937 patients, 685 patients with ACLF who fulfilled the CLIF-C ACLF definitions were finally enrolled and evaluated.

Definition of ACLF and the scoring systems

The detailed diagnostic criteria for organ failure and the definition of the CLIF-C ACLF score have been described previously [1]. The grade of ACLF was based on the CLIF-C Organ Failure (CLIF-C OF) criteria and included 6 failing organs/processes (the liver, kidney, brain, coagulation, circulation, and respiration) [1]. The CLIF-C ACLF score was computed using the following formula [5]:

$$\text{CLIF-C ACLF score} = 10 \times (0.33 \times \text{CLIF-OF score} + 0.04 \times \text{age} + 0.63 \times \ln[\text{WBC counts}] - 2)$$

Data collection

Parameters, including baseline demographic and laboratory data, perioperative variables for evaluating risk scores, and survival, were collected from the fully computerized database extraction software. Since ACLF is a dynamic disease that can rapidly change over time [6], all the data required to compute the risk scores were updated at the time of LT when variables were measured repeatedly.

To adjust short-term mortality with pre-LT comorbidities, we employed the revised cardiac risk index (RCRI), which is the most frequently validated model for perioperative cardiac risk stratification and is recommended by many guideline committees [7]. The variables included in the RCRI are as follows (worth 1 point each): history of ischemic heart disease, congestive heart failure, cerebrovascular disease, high-risk surgery (i.e., liver transplant), preoperative insulin use, and preoperative creatinine level > 2 mg/dl [7,8].

Study outcomes

Mortality data were collected up to February 2020 (i.e., at least 1 year from the date of LT) from the medical record database and the Organ Transplantation Center. The main study outcomes were all-cause mortality at 28 and 90 days after LT.

Statistical analysis

In a univariate statistical analysis, the chi-square test or Fisher's exact test was used for categorical variables, whereas Student's *t*-test and the Mann-Whitney test were used for continuous variables, as appropriate. Based on the liver disease severity index of the model for end-stage liver disease for sodium (MELD-Na) score, the trajectory of the total and differential WBC counts was traced. To evaluate the association of the total and differential WBC counts with short-term mortality, a multivariable Cox proportional hazards regression analysis with backward elimination was performed. Relevant perioperative variables, including MELD-Na score, age, male sex, RCRI, massive transfusion, and WBC and differential counts, were used to calculate adjusted hazard ratios (HRs).

The cubic spline interpolation for HR was performed to

represent the changes in risk for 90-day mortality across the entire spectrum of the total and differential WBC counts, treated as a continuous metric. Variables are expressed as numbers (percentages), means ± standard deviations, or medians (interquartile ranges [IQRs]) as appropriate.

RESULTS

Baseline characteristics of patients with ACLF

The median age of patients with ACLF (n = 685) was 52 (IQR, 44, 57) years, and 71.4% were men with MELD-Na and CLIF-C ACLF scores of 32 (IQR, 27, 39) and 45.7 (IQR, 39.2, 53.0), respectively (Table 1). A total of 400 (58.4%) and 285 (41.6%) patients underwent living-donor LT and deceased-donor LT, respectively.

RCRI in patients with ACLF

Although the RCRI was higher in patients with ACLF compared to those without ACLF, no significant difference was observed between these two populations of patients following multivariable Cox regression analysis. These results suggested a limited impact of RCRI on short-term mortality in

Table 1. Patients' Demographics according to Acute-on-chronic Liver Failure

Variable	No ACLF (n = 2,252)	ACLF (n = 685)	Total (n = 2,937)	P value
Demographic data				
Age (yr)	54 (49, 59)	52 (44, 57)	54 (48, 59)	< 0.001
Sex (men)	1,755 (77.9)	489 (71.4)	2,244 (76.44)	< 0.001
Body mass index (m/kg^2)	24.3 (22.3, 26.5)	24.1 (21.5, 26.7)	24.2(22.1, 26.6)	0.161
Diabetes	572 (25.4)	140 (20.4)	712 (24.2)	0.009
Hypertension	407 (18.1)	96 (14.0)	503 (17.1)	0.016
MELD score	12 (9, 16)	32 (26, 39)	14 (9, 22)	< 0.001
MELD_Na score	12 (9, 17)	32 (27, 39)	14 (9, 24)	< 0.001
CLIF-C ACLF score	29.4 (26.5, 32.3)	45.7 (39.2, 53.0)	30.9 (27.4, 36.3)	< 0.001
RCRI				< 0.001
1	1,702 (75.6)	337 (49.2)	2,039 (69.4)	
2	474 (21.0)	263 (38.4)	737 (25.1)	
3	72 (3.2)	73 (10.7)	145 (4.9)	
4	4 (0.2)	11 (1.6)	15 (0.5)	
5	0 (0.0)	1 (0.1)	1 (0.0)	
Hepatic encephalopathy	149 (6.6)	319 (46.6)	468 (15.9)	< 0.001
Hydrothorax	216 (9.6)	180 (26.3)	396 (13.5)	< 0.001
Laboratory variables				
Total bilirubin (mg/dl)	1.5 (0.9, 2.8)	23.9 (13.3, 34.0)	2 (1.0, 6.4)	< 0.001
Creatinine (mg/dl)	0.76 (0.63, 0.90)	1.11 (0.70, 2.07)	0.8 (0.64, 1.00)	< 0.001
Lactic acid (mmol/L)	1.8 (1.4, 2.3)	2.2 (1.7, 3.0)	1.9 (1.5, 2.5)	< 0.001
Prothrombin time (INR)	1.3 (1.2, 1.5)	2.3 (1.8, 2.8)	1.4 (1.2, 1.8)	< 0.001
Preoperative therapy				
Vasopressor support	0 (0.0)	118 (17.2)	118 (4.0)	< 0.001
Mechanical ventilation	0 (0.0)	155 (22.6)	155 (5.3)	< 0.001
Renal replacement therapy	11 (0.5)	184 (26.9)	195 (6.6)	< 0.001
Operative variables				
Cold ischemic time (min)	82 (66, 99)	110 (76, 238)	85 (68, 108)	< 0.001
Warm ischemic time (min)	40 (33, 49)	44 (36, 52)	41 (34, 50)	< 0.001
Total ischemic time (min)	123 (105, 145)	159.00 (118, 290)	128 (108, 156)	< 0.001
Massive transfusion, (≥ 10 units)	806 (35.8)	561 (81.9)	1,367 (46.5)	< 0.001

Values are presented as median (1Q, 3Q) or number (%). ACLF: acute-on-chronic liver failure, MELD score: model for end-stage liver disease score, MELD_Na score: sodium-adjusted model for end-stage liver disease score, CLIF-C ACLF score: chronic liver failure consortium acute-on-chronic liver failure score, RCRI: revised cardiac risk index, INR: international normalized ratio.

Table 3. Comparison of Total and Differential White Blood Cell Counts in Patients with and without Acute-on-chronic Liver Failure

Variable	No ACLF (n = 2,252)	ACLF (n = 685)	P value
Total WBC (/μl)	3,300 (2,400, 4,400)	6,200 (4,100, 9,800)	< 0.001
Neutrophils (%)	56.3 (47.8, 64.3)	72.8 (63.4, 80.3)	< 0.001
Lymphocytes (%)	28.0 (20.2, 36.1)	12.6 (7.8, 19.8)	< 0.001
Monocytes (%)	10.6 (8.5, 13.2)	11.2 (8.1, 14.6)	0.116
Eosinophils (%)	3.1 (1.8, 4.9)	1.7 (0.8, 2.9)	< 0.001
Basophils (%)	0.5 (0.3, 0.7)	0.3 (0.2, 0.5)	< 0.001
NLR (%)	2.0 (1.3, 3.2)	5.8 (3.2, 10.1)	< 0.001
LMR (%)	2.5 (1.7, 3.6)	1.2 (0.8, 1.8)	< 0.001

Values are presented as median (1Q, 3Q). ACLF: acute-on-chronic liver failure, WBC: white blood cell, NLR: neutrophil-to-lymphocyte ratio, LMR: lymphocyte-to-monocyte ratio.

Table 2. Cox Regression Analysis of Risk Factors with 90-day Mortality in Patients with Liver Transplantation

Variable	Univariable analysis		Multivariable analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
MELD-Na score	1.03 (1.00–1.06)	0.030		
RCRI				
2	1.84 (1.07–3.14)	0.026		
≥ 3	2.53 (1.30–4.91)	0.006		
Age (per 1 year increase)	1.03 (1.01–1.06)	0.010		
Male sex	0.61 (0.38–0.99)	0.045	0.56 (0.34–0.91)	0.019
Diabetes	1.29 (0.75–2.24)	0.355		
Hypertension	0.78 (0.38–1.64)	0.519		
Massive transfusion (≥ 10 vs. < 10 RBC units)	3.74 (1.36–10.28)	0.010	3.15 (1.14–8.68)	0.026
NLR (per 1%)	1.03 (1.02–1.05)	< 0.001		
Total WBC count (per × 10^3/μl)	1.02 (0.98–1.06)	0.346		
Neutrophil (per 1%)	1.05 (1.03–1.08)	< 0.001	1.04 (1.02–1.07)	0.001
Lymphocyte (per1%)	0.93 (0.90–0.97)	< 0.001		
Monocyte (per 1%)	0.93 (0.88–0.99)	0.016		
Eosinophil (per 1 %)	0.89 (0.78–1.03)	0.117		
Basophil (per 1%)	0.32 (0.12–0.86)	0.024		

HR: hazard ratio, CI: confidence interval, MELD_Na score: sodium-adjusted model for end-stage liver disease score, RCRI: revised cardiac risk index, RBC: red blood cell, NLR: neutrophil-to-lymphocyte ratio, WBC: white blood cell.

patients with ACLF (Tables 1, 2).

Total and differential WBC counts

Total WBC counts were higher in patients with ACLF compared to those without ACLF (6,200 [4,100, 9,800] vs. 3,300 [2,400, 4,400], P < 0.001). The neutrophil ratio was also elevated in patients with ACLF (72.8% [63.4, 80.3]) compared to those without ACLF (56.3% [47.8, 64.3], P < 0.001). In patients with ACLF, the ratios of lymphocytes, eosinophils, and basophils decreased, whereas the monocyte ratio was comparable to that in patients without ACLF (Table 3).

Trajectory of total and differential WBC counts as a function of liver disease severity

Upon plotting the total WBC count and differential counts in relation to the severity of liver disease, the total WBC counts showed a sigmoid pattern. However, the neutrophil ratio demonstrated a relatively linear trend compared with that of the WBC counts (Fig. 1).

Continuous HR for 90-day mortality as a function of WBC counts and neutrophil ratio

With a rising MELD-Na score in patients with ACLF, the

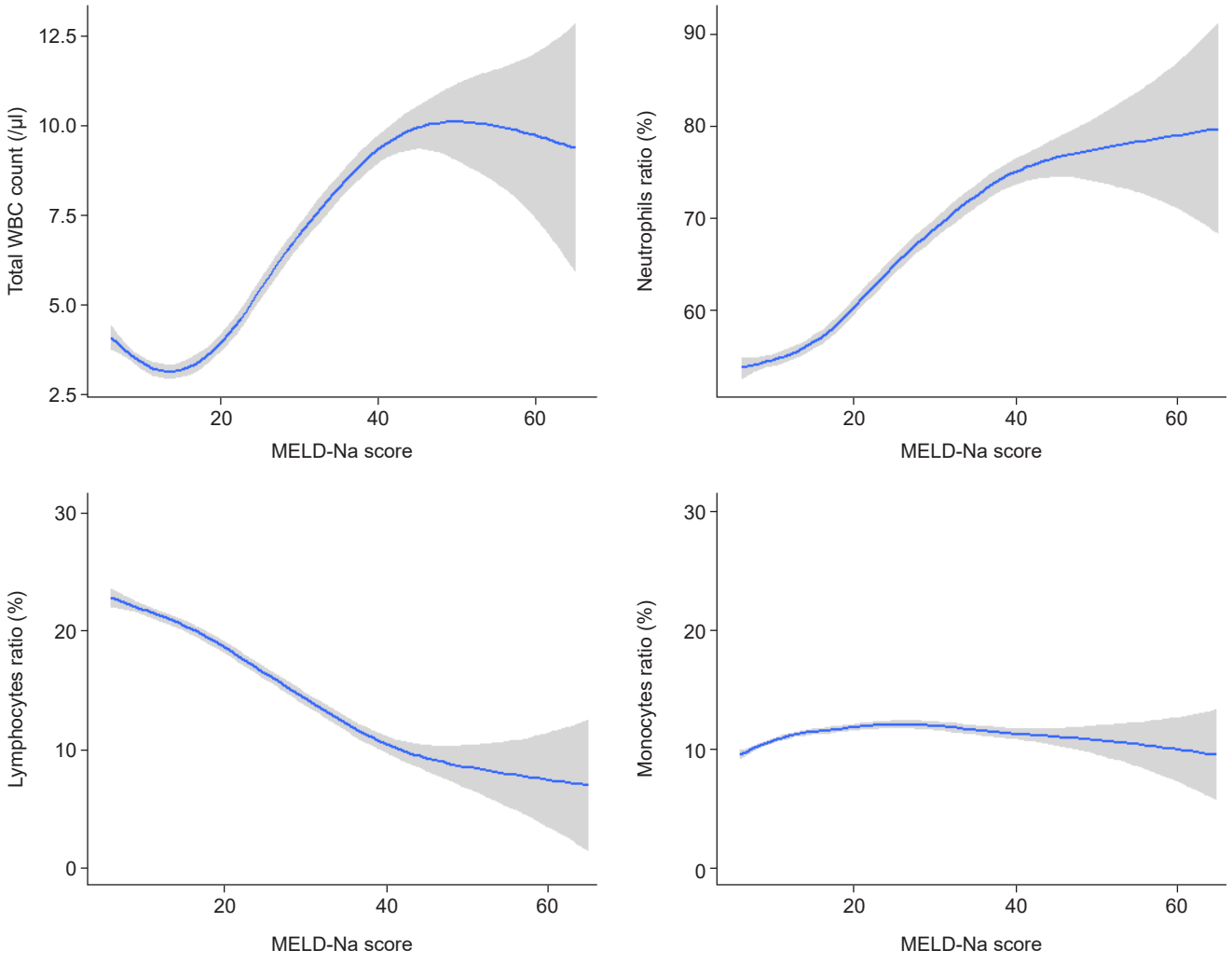

Fig. 1. The trajectory of the total and differential (neutrophils, lymphocytes, and monocytes) WBC counts as a function of the severity of liver disease. WBC: white blood cell, MELD_Na score: sodium-adjusted model for end-stage liver disease score.

HR of 90-day mortality increased concurrently with the neutrophil ratio; however, the total WBC counts exhibited a non-linear shape and plateaued pattern with the increase in the WBC counts (Fig. 2).

Multivariable Cox regression analysis

In the univariate analysis, MELD-Na score, RCRI, age, sex, massive transfusion, and ratios of neutrophil, lymphocyte, monocyte, and basophil remained significant for the post-LT 90-day mortality. Of these variables, massive transfusion, sex, and the ratios of neutrophils remained significant even after undergoing multivariate adjustment via a backward elimination process. Only the neutrophil ratio remained significant (HR, 1.04 [1.02–1.07]; P = 0.001) among the differential counts. In contrast, neither the univariate (HR, 1.02 [0.98-1.06]; P = 0.346) nor the multivariate Cox analysis of 90-day post-LT mortality showed a significant relationship between the total WBC counts and mortality (Table 2).

DISCUSSION

This study evaluated the prognostic value of the total and differential WBC counts for short-term mortality following LT in patients with ACLF. The results of this study emphasized the importance of neutrophilia over leukocytosis in predicting short-term mortality after LT. ACLF is characterized by overwhelming systemic inflammation and increased susceptibility to infections [4,9]. Neutrophils, as the most abundant type of WBCs, play a vital role in the immune re-

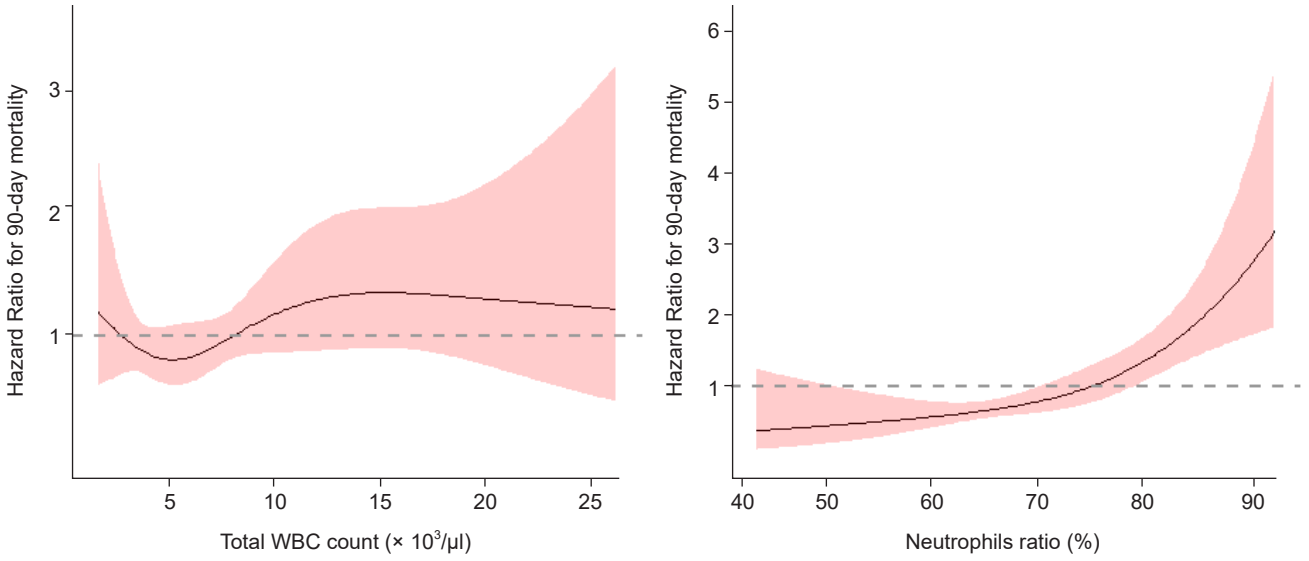

Fig. 2. Cubic spline curves of the hazard ratio for 90-day mortality following liver transplantation in patients with acute-on-chronic liver failure: total WBC counts vs. neutrophils ratio. WBC: white blood cell.

sponse and have been implicated in various inflammatory and pathological processes associated with ACLF [10].

In the current study, the neutrophil ratio demonstrated a relatively linear trend with an increasing MELD-Na score, whereas the total WBC counts exhibited a sigmoid pattern. Furthermore, the total WBC counts plateaued and subsequently decreased at a significantly high MELD-Na score, indicating that the total WBC counts may not be a valid biomarker for assessing liver disease severity and predicting short-term post-LT mortality in patients with ACLF.

Our finding related to the impact of neutrophilia on short-term post-LT mortality has clinical implications; clinicians will be able to make informed decisions regarding patient prioritization for LT. Furthermore, by including the assessment of the levels of neutrophils in patients, high-risk patients can be more accurately identified. Hence, we suggest that, instead of the total WBC counts, the neutrophil count data should be included in the CLIF-C ACLF score to enhance its predictive accuracy.

The evaluation of differential WBC counts is crucial to understand the body's defense against pathogens and injury [11]. In patients with ACLF, the immunological aspect of inflammation is a central component in the progression of liver disease, and various WBC subtypes play critical roles in the inflammatory process [10]. Neutrophils are the first WBC types to arrive at the site of inflammation or infection and are the key to the response against invading pathogens/toxins [12]. In general, it is widely believed that neutrophilia may be a more definite immune response to specific infections, tissue damage, or inflammation [11].

In ACLF, it is essential to consider the roles of different WBC subtypes in the immune response and inflammation [4,10]. Neutrophils, eosinophils, basophils, monocytes, and lymphocytes contribute to the body's defense system in distinct ways. For instance, neutrophils and monocytes/macrophages are crucial in the initial stages of inflammation and infection, whereas lymphocytes, including T and B cells, are responsible for the adaptive immune response [11]. However, it should be noted that patients with ACLF exhibit neutrophilia along with defective immune function [10].

Patients with ACLF exhibit dysregulation of specific circulating immune cells, including increased neutrophils and monocytes (leukocytosis) and decreased lymphocyte counts owing to a depletion of memory lymphocytes (B cells, CD4 T-cell lineages, CD8 T cells, and natural killer cells) [10,13]. Previously, it was also suggested that the increase in blood neutrophils during ACLF is possibly partly a result of the mobilization of a marginated pool of neutrophils [14]. Nevertheless, it is more accurate to characterize neutrophilia as a consequence of the stimulation of a hematopoietic response program called emergency granulopoiesis [12]. Patients with ACLF exhibit elevated systemic levels of stimuli for emergency granulopoiesis, such as lipopolysaccharides and cytokines, including granulocyte colony-stimulating factor, interleukin-1, and tumor necrosis factor-α [9,15].

A recent study has provided further insights into the im-

munological aspects of ACLF [10]. The dysregulation of blood immune cells in patients with ACLF, characterized by neutrophilia and increased proportions of macrophages (M0-like monocytes), underscores the importance of investigating neutrophils. Therefore, the distinctive neutrophil phenotype, poor antimicrobial activities, and changes in lymphocyte subsets detected in patients with ACLF contribute to the neutrophilia but immunosuppressed state [9,10,15].

Future research should be directed toward investigating the complex immune dysregulation during ACLF, particularly neutrophilia and defective immunological function. Functional studies on neutrophils would help elucidate their roles in ACLF pathogenesis and progression and the mechanisms behind the impaired function of neutrophils. Furthermore, investigating the effects of various treatments on neutrophil function can lead to novel therapeutic approaches for ACLF.

This study had a few limitations. The data were collected retrospectively from a single center, and the sample size may not be representative of all populations of patients with ACLF. Additionally, further research is required to determine the association between the predictive relevance of neutrophilia and its impaired immunological capacity for long-term survival.

In conclusion, our study demonstrated that neutrophilia is more predictive than the elevated total WBC counts for short-term mortality after LT in patients with ACLF. This study highlights the significance of understanding the immunological aspects of ACLF, particularly the role of neutrophils and their possible defective immune function. Further research is needed to validate these findings in larger cohorts and explore the underlying mechanisms connecting neutrophils to ACLF pathophysiology to improve patients' post-LT survival.

FUNDING

This research was supported partly by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute, funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HR20 C0026).

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

Conceptualization: Won-Jung Shin, Jun-Gol Song, Gyu-Sam Hwang. Data curation: Kyoung-Sun Kim, Young-Jin Moon, In-Gu Jun. Formal analysis: Kyoung-Sun Kim, Jae-Hwan Kim, Hye-Mee Kwon, Won-Jung Shin. Methodology: Jae-Hwan Kim, Young-Jin Moon, Sung-Hoon Kim. Visualization: Hye-Mee Kwon. Writing - original draft: Kyoung-Sun Kim. Writing - review & editing: Gyu-Sam Hwang. Investigation: Sung-Hoon Kim. Supervision: Won-Jung Shin, In-Gu Jun, Jun-Gol Song, Gyu-Sam Hwang. Validation: Gyu-Sam Hwang.

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