Clinical Trial/Experimental Study

Medicine

OPEN

MAIT cells predict long-term prognosis in liver failure patients

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Abstract

Background: Liver failure (LF) is a life-threatening clinical syndrome characterized by intense systemic inflammation and organ failure(s), leading to a high mortality rate. The pathogenesis of LF is multifactorial, immune response, and gut bacterial translocation are thought to be major contributing factors. Mucosal-associated invariant T (MAIT) cells play a critical role in immune response and gut bacterial translocation. We aimed to investigate changes of the MAIT cell ratio in patients with LF and to explore the predictive value for long-term prognosis in patients with LF.

Material and Method: We recruited 75 patients with LF from Nantong Third People's Hospital, isolated peripheral blood mononuclear cells, and detected the proportion of circulating MAIT cells by flow cytometry. Statistical analyses were performed using the GraphPad Prism software.

Results: Our data showed that the proportion of MAIT cells alterations was independent of the cause of viral infection in patients with LF. Kaplan-Meier survival analysis showed that LF patients with low level of MAIT cells had poor long-term prognosis. The area under the receiver operating characteristic curve of the MAIT cell proportion was larger than that of the Model for End-Stage Liver Disease (MELD) score. More importantly, the combination of MAIT cell proportion and MELD score had a better effect in predicting long-term prognosis of LF patients than any single index (AUC = 0.91, 95% CI:0.84–0.97), and multivariate logistic regression analysis indicated that the circulating MAIT cell proportion was an independent risk factor for LF.

Conclusion: The proportion of MAIT cells in PBMC is an outstanding predictor for the long-term prognosis in patients with LF.

Abbreviations: ACLF = chronic and acute liver failure, AFP = alpha-fetoprotein, ALF = acute liver failure, ALT = alanine aminotransferase, APC = allophycocyanin, AST = aspartate aminotransaminase, AUC = Area Under Curve, CI = Confidence Interval, CLF = chronic liver failure, FITC = fluorescein isothiocyanate, IL = interleukin, LF = liver failure, MAIT cell = Mucosal-associated invariant T cell, MELD = Model for End-Stage Liver Disease, PBMCs = peripheral blood mononuclear cells, PE = phycoerythrin, rcf = relative centrifuge force, ROC = receiver operating characteristic, SALF = subacute liver failure, TCR = T-cell receptor.

Keywords: liver failure, mucosal-associated invariant T cells, prognosis.

1. Introduction

Liver failure (LF) is a clinical syndrome characterized by acute and severe hepatic derangements resulting from various insults, resulting in organ failure and high mortality.[1] Based on the characteristics of onset and rate of disease progression, LF can be divided into 4 categories: acute liver failure (ALF), subacute liver failure (SALF), chronic and acute liver failure (ACLF), and chronic liver failure (CLF).[2] Moreover, LF is a progressive disease associated with rapid clinical deterioration and high mortality, with a short-term fatality rate as high as 50%–90%, and early prediction of mortality and intervention can improve the prognosis of patients.

The pathogenesis of LF is multifactorial and is related to interactions between the immunoinflammatory system, microbiota, and various precipitating factors.[3] Among these factors, the

TCC and HX contributed equally to this work.

Funding: This work was supported by the Nantong Health Bureau Scientific Research Fund Project (MB2019023), the National Natural Science Foundation of China (Grant No. 81600449), 6 Peak Talents in Jiangsu Province (YY-177), the Project of Jiangsu Province Youth Medical Talent Development (QNRC2016400), the Project of Nantong Youth Medical Talent Development (No. 05), the 333 Engineering Project in Jiangsu Province, the project of Nantong Health Bureau Scientific Research Fund Project (MA2020017), and the project of Nantong Science and Technology (JCZ20077).

The authors have no conflicts of interest to disclose.

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

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How to cite this article: Cheng T-C, Xue H, Li H, Liu Y-C, Tian L-J, Bian Z-L, Chen F-S. MAIT cells predict long-term prognosis in liver failure patients. Medicine 2022,101:34(e29809).

Received: 29 December 2021 / Received in final form: 5 May 2022 / Accepted: 27 May 2022

http://dx.doi.org/10.1097/MD.0000000000029809

immune response and gut bacterial translocation are thought to be major contributing factors.[4, 5] Zhao et al[6] reported that T-cell-mediated immune injury plays a critical role in the pathogenesis of hepatitis B virus-related LF. Chronic stimulation of both innate and adaptive immune cells contributes to this process.[7] Innate immune cells can be activated by cytokines, bacteria, and endotoxins from the gut, which reach the liver via the portal vein, particularly in patients with advanced liver disease.[8] Mucosal-associated invariant T (MAIT) cells are unique innate-like T cells that bridge innate and adaptive immunity.[9, 10] The intestinal microbiome plays a key role in the development of certain subsets of innate-like T cells, such as MAIT cells.[11, 12] MAIT cells are characterized by the invariant T-cell receptor (TCR) chain Vα7.2-Jα33 and are restricted by MR1, they are abundant in mucosal tissues and peripheral blood and are highly enriched in the human liver.[13] Since MAIT cells respond to a wide range of bacteria, their importance in microbial immunity is being increasingly recognized.[14] It has been reported that MAIT cells are important in antibacterial immunity at mucosal sites and play important roles in host defense against bacterial and viral infections.[13] MAIT cells recognize derivatives of bacterial riboflavin metabolites and are important effector cells in mucosal immunity, their development can be influenced by the intestinal microbiome.[15] MAIT cells act in the gut by inducing dysbiosis of the microbiota and the loss of gut integrity.[12] We proposed that MIAT cell might be important linker between host immunity and gut microbiota dysbiosis and integrity in LF. Our previous research found that circulating MAIT cells were significantly decreased in HBV-related liver failure patients compared to healthy volunteers.[16]

Mounting evidence suggests that MAIT cells play complex roles in regulating various liver diseases, including nonviral hepatopathies (such as autoimmune liver disease,[17], alcoholic or nonalcoholic fatty liver disease, and hepatocellular carcinoma[18]) and viral hepatopathies (such as hepatitis B virus infection[19] and chronic hepatitis C or D[20–22]). Many researchers have reported an obvious decrease in circulating MAIT cell level, but the reason for this change remains unclear.[21] Some researchers have speculated that this decrease could be attributed to apoptosis or cell exhaustion. A recent study reported that in patients with decompensated liver cirrhosis, MAIT cell levels were decreased in the circulation but enriched and highly activated in ascites; the study also showed that MAIT cells were highly responsive to bacterial stimulation, suggestive of active homing of MAIT cells to the site of infection.[23] Therefore, MAIT cell variation may be due to the specific microenvironment of the disease itself caused by microbial translocation and immunoinflammatory reaction conditions and is also associated with microbial infection including bacteria and virus. Our previous study illustrated a significant decline in circulating MAIT cells in patients with HBV-related LF, and we showed that the reduction in MAIT cell levels may be due to stimulation by interleukin (IL)-12 and IL-18.[16] However, alterations in MAIT cells in nonHBV-infected liver failure patients are not clear, nor are the alterations in MAIT cells due to other causes. In this study, we investigated MAIT cell alterations in all LF patients regardless of the cause, and we also focused on the long-term predictive value of the MAIT cell ratio in the prognosis in patients with LF. Additionally, we will have some new findings that are different from our previous research.

2. Materials and Methods

2.1. Patients

After approval of the project by the Ethical Committee of Nantong Third People's Hospital, 75 LF inpatients were recruited, and the recruitment period for the study was from September 1, 2018, to December 31, 2019. LF was defined according to the guidelines.[1] The exclusion criteria were as follows: age <18 or >75 years, patients with microbial infection, human immunodeficiency virus, and liver cancer, previous history of immunomodulatory therapy, pregnant and lactating women, and patients with other serious diseases such as heart, brain, lung, and kidney diseases. All subjects provided written informed consent in accordance with the institutional review board guidelines for the protection of subjects. The research process is presented in a flowchart (Fig. 1), and the baseline data are presented in Table 1.

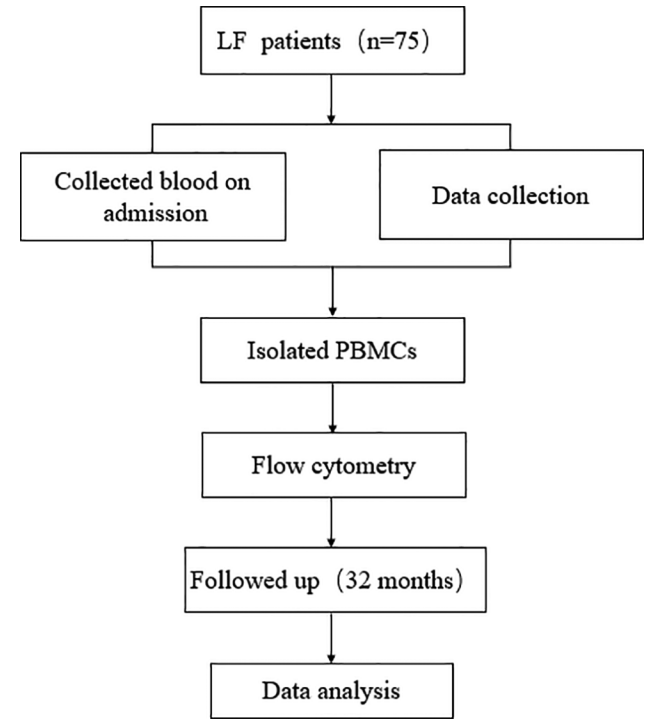

Figure 1. Flowchart of LF patients enrolled in the study. Flowchart showing the process from enrolling patients and follow up for final analysis. LF = liver failure.

2.2. Isolation of peripheral blood mononuclear cells from the blood

The isolation of peripheral blood mononuclear cells (PBMCs) by density centrifugation was performed as previously described.[24] In brief, 5 mL of peripheral blood was added on 3 mL Ficoll and centrifuged for 30 minutes at 860 relative centrifuge force (rcf) at 20 °C. The interphase layer was collected and washed with phosphate-buffered saline. PBMCs were collected by centrifugation for 10 minutes at 300 rcf and stored in fetal bovine serum (Cell Sciences, Canton, MA) supplemented with 10% dimethyl sulfoxide (Beyotime Biotechnology, Shanghai, China) in liquid nitrogen for further analysis.

2.3. Flow cytometry

Flow cytometry was performed according to standard protocols using the following antibodies: antiTCRVα7.2-phycoerythrin (PE) (BD Biosciences, Franklin Lakes, NJ, United States), antiCD3-fluorescein isothiocyanate (FITC) (BD Biosciences), and antiCD161-allophycocyanin (APC) (BD Biosciences). The phenotype of MAIT cells was defined as $CD3^+CD161^+TCR\ V\alpha7.2^+$. Isotype-matched control antibodies were used as negative controls. Flow cytometry analysis was performed using a BD FACS Calibur (BD Biosciences). Data were analyzed using FlowJo software (TreeStar, San Carlos, CA). The proportion of MAIT cells to $CD3^+$ T cells was used for further analysis.

Table 1

Baseline characteristics of liver failure (LF) patients.

Clinical variables	LF
Number	75
Age (years)	a
Male (n)	46
Alanine aminotransferase (U/L)	500.12 ± 652.26
Aspartate aminotransaminase (U/L)	444.33 ± 540.77
Total bilirubin (μmol/L)	293.69 ± 144.52
Albumin (g/L)	30.87 ± 4.26
Cholinesterase (U/L)	3272.52 ± 2144.50
Prothrombin time (s)	24.98 ± 7.59
International normalized ratio	2.19 ± 0.68
Prothrombin activity (%)	30.23 ± 8.69
Leukocyte count ($\times 10^9$/L)	6.54 ± 3.88
Lymphocyte count ($\times 10^9$/L)	2.52 ± 4.71
Blood platelet count ($\times 10^9$/L)	103.32 ± 61.18
Creatinine (μmol/L)	102.84 ± 147.00
Hypersensitive C-reactive protein (mg/dl)	17.33 ± 20.03

All data are presented as the mean ± SD.

2.4. Statistical analysis

Statistical analysis of clinical data was performed using unpaired Student t-tests. ROC curve and area under the curve (AUC) analyses were used to establish the prognostic value of MELD score and MAIT cell proportion. Multivariate logistic regression analysis was performed to identify independent risk factors that affect the prognosis of patients with LF. Statistical evaluations were performed using GraphPad Prism software (version 8.0, La Jolla, CA), and $P < 0.05$ was considered statistically significant. All data are presented as mean ± standard deviation (SD).

3. Results

3.1. Patient characteristics

Seventy-five patients with LF and 20 healthy controls were included in this study. The demographic and clinical characteristics of the patients with LF are summarized in Table 1. Of the 75 patients, ages ranged from 22 to 71 years, and male patients accounted for 61% (46/75).

3.2. The changes in the circulating MAIT cell proportion were independent of viral infection.

MAIT cells are defined as $CD3^+CD161^+TCR\ V\alpha7.2^+$ cells in humans. The flow cytometry strategy to identify MAIT cells is presented in Figure 2A. we divided the LF patients into nonvirus-infected (n = 20) groups and virus-infected (n = 55, including HBV or HCV infection) groups based on the cause. The results showed that there was no significant difference in the proportion of CD3 cells between healthy control (54.67 ± 3.66) and the 2 groups of patients (53.78 ± 3.63 vs 57.08 ± 2.29, $P > 0.05$) (Fig. 2B). After further comparing the percentage of MAIT cells in the CD3+ T cell population, we found that the proportion of MAIT cells was no difference between the virus group and the nonvirus group (1.55 ± 0.66 vs 1.76 ± 0.92, $P > 0.05$) in LF patients (Fig. 2C), suggesting that the alterations in circulating MAIT cells are not dependent on viral infection in LF patients. In addition, we detected the proportion of MAIT cells in healthy controls and compared the results with those of patients with LF. The data shown that the proportion of MAIT cells was decreased in nonvirus or virus LF patients compared with healthy controls (5.03 ± 0.54 vs 1.55 ± 0.66, $P < 0.0001$, 5.03 ± 0.54 vs 1.76 ± 0.92, $P < 0.0001$) (Fig. 2C).

Decreased frequencies of MAIT cells predicted a worse outcome for LF patients

The patients were followed up for 960 days. Based on the MAIT cell percentage, the patients were classified into 2 groups: the group with high level of MAIT cells and the group with low level of MAIT cells. Significant differences were found by Kaplan-Meier survival analysis, which predicted that LF patients with low level of MAIT cells had poor long-term prognosis ($P < 0.0001$) (Fig. 3A).

MAIT cell ratio combined with MELD score has better effect in predicting the prognosis of LF patients than single index.

The ROC curve analysis was performed to compare the long-term predictive value of MAIT cell proportion with MELD score for LF patients, data showed that the area under the ROC curve (AUC) was 0.78 (95% CI:0.67–0.89) and 0.83 (95% CI:0.73–0.92) for MELD score and MAIT cell ratio, and the AUC of their combined detection was 0.91 (95% CI:0.84–0.97) (Fig. 3B). The sensitivity of the MELD score, proportion of MAIT cells, and their combined detection in LF patients were 73.33%, 73.33%, and 83.33%, respectively, and the specificity were 75.56%, 80.00%, and 86.67%, respectively (Table 2). The results of ROC curve analysis demonstrated that the proportion of MAIT cells was superior to the MELD score in predicting the long-term prognosis of patients with LF. In addition, the sensitivity and specificity of the MAIT cell ratio combined with MELD score detection were significantly higher than those of any single-index test.

3.3. MAIT cell proportion as an independent risk factor for LF

The variables were screened for inclusion in a univariate logistic regression model to test for risk factors for LF. As shown in Table 3, the data showed that MAIT cell proportion, age, cholinesterase, prothrombin activity, creatinine, and MELD score were significant risk predictors of LF by univariate analysis ($P = .007$, $P = .047$, $P = .048$, $P = .002$, $P = .032$, and $P = .001$, respectively) (Table 3). After fully eliminating confounding factors, the multivariate logistic analysis further showed that the proportion of MAIT cells was an independent risk factor affecting the prognosis of patients with LF (Table 4).

4. Discussion

This study is the first analysis of MAIT cells in LF patients independent of the cause and investigated whether MAIT cell proportion in LF patients is dependent on the cause of disease. MAIT cell levels have also been demonstrated to decrease in patients with alcoholic liver disease, nonalcoholic fatty liver disease,[20] primary biliary cholangitis,[25] and viral infectious diseases such as infection with HBV, HCV, HDV, or HIV.[19, 26] Different viral infections (such as HBV[27] and HCV[22] infection) cause a significant reduction in MAIT cell levels. Based on these studies, the number of MAIT cells decreased in chronic hepatitis independent of the cause. However, there have been no reports of liver failure. To clarify whether MAIT cell changes are related to viral infection in LF, we compared the MAIT cell percentage between virus-infected and nonvirus-infected LF patients and found no differences between them, indicating that the changes in circulating MAIT cells in LF patients were not related to viral infection. Many remarkable studies have suggested that the alteration of MAIT cells may be due to the specific immune milieu and gut bacterial translocation in liver disease,[28, 29] which are the major pathogenesis in LF. We speculated that alteration in the proportion of MAIT cells in LF is associated with immune status.

Previous studies have mentioned a lack of predictive prognostic biomarkers for LF.[5] The MELD score is a commonly

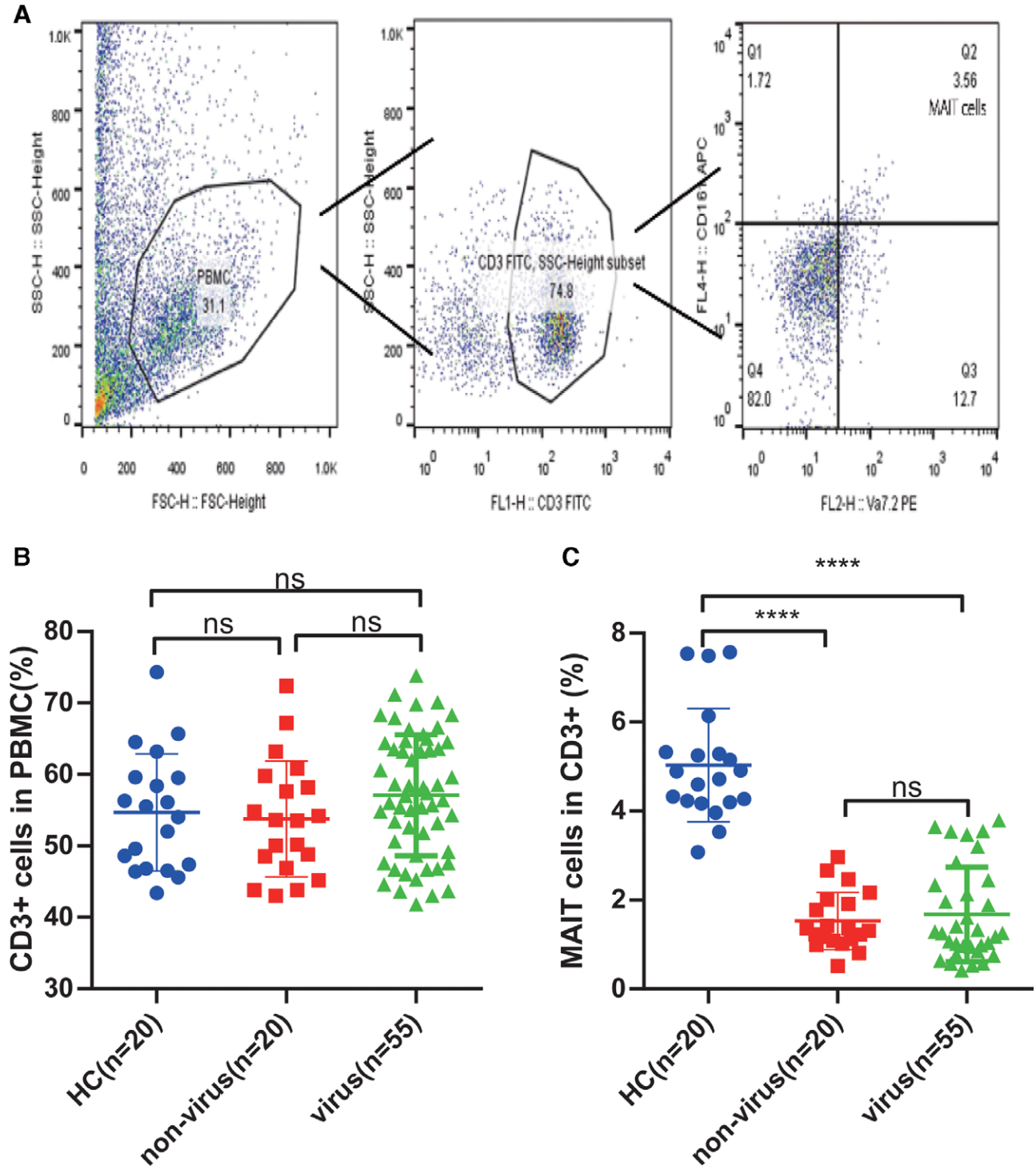

Figure 2. Proportion of CD3 positive or Mucosal-associated invariant T (MAIT) cells in healthy controls and LF patients. A: The flow cytometry strategy of mucosal-associated invariant T (MAIT) cells in Peripheral blood mononuclear cell (PBMC). B: There were no difference in proportion of CD3+ cells between healthy controls and nonvirus or virus LF. C: The proportion of MAIT cells in LF patients decreased compared with healthy controls independent of the virus or not. ns, no significance, $^{****}P < 0.0001$.

recognized prognostic indicator for liver failure, but it is overly complex and has limited application value. Owing to the poor prognosis of LF, finding a more accurate and convenient long-term prognostic marker for clinical application is needed to identify patients who should undergo liver transplantation early. At present, the pathogenesis of LF has not been fully clarified, but most researchers believe that immune-mediated damage plays a key role.[30] T cell-mediated immune responses have been reported to play a vital role in the pathogenesis of LF. MAIT cells are an important component of T cell immunity. We found that LF patients with a low proportion of MAIT cells survive for a short term compared to patients with a high ratio, which indicates that host immune status affects the prognosis of patients with LF. Our data showed that the area under the ROC curve for the MAIT cell proportion was

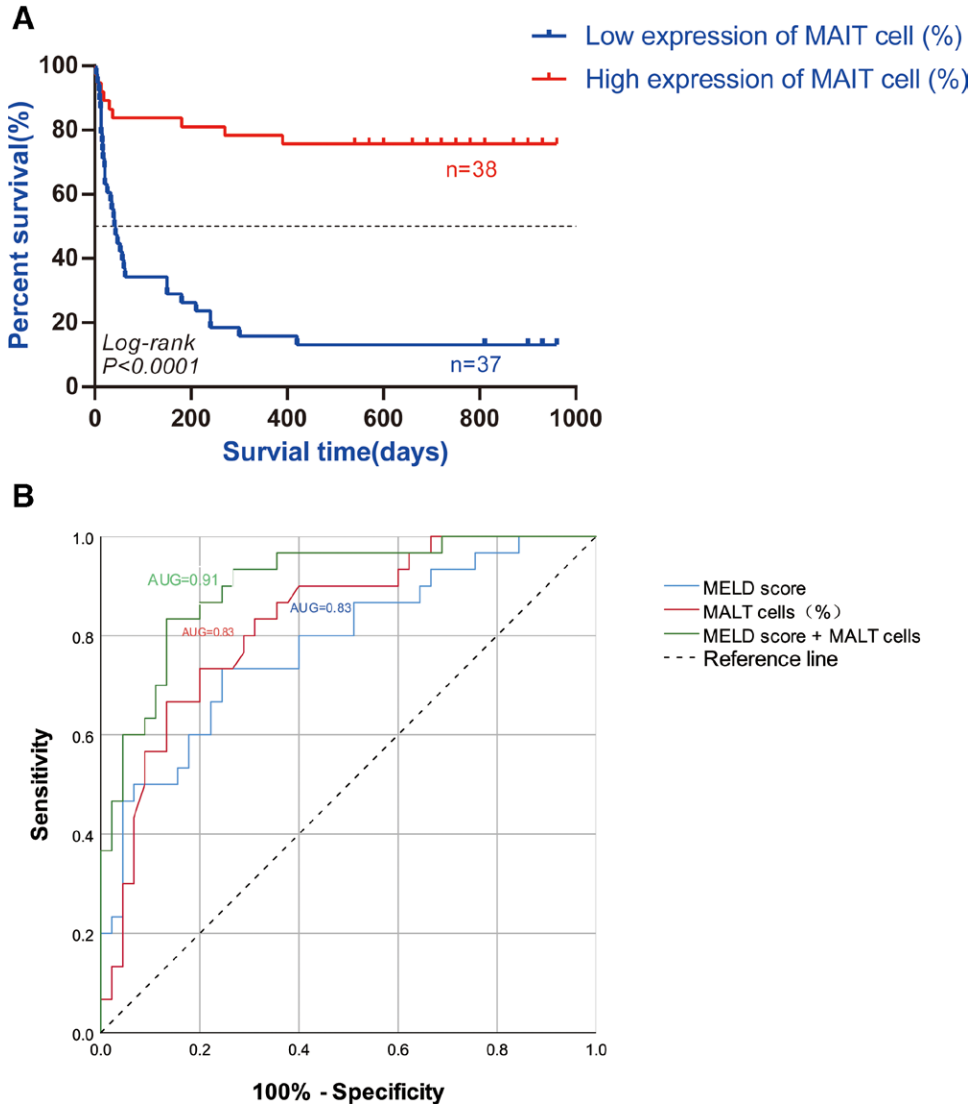

Figure 3. Lower frequency of mucosal-associated invariant T (MAIT) cells predicted a worse long-term prognosis for LF patients. A: The Kaplan-Meier curve for LF patients with low (n = 38) or high (n = 37) level of MAIT cells. B: The receiver operating characteristic (ROC) curves of the model for end-stage liver disease (MELD) score, MAIT cell proportion (%), and MELD score combined with MAIT cell proportion (%). AUC: area under the curve.

Table 2

Area under the ROC curve analysis of MELD scores, proportion of mucosal-associated invariant T (MAIT) cells, and their combination in predicting long-term prognosis for liver failure (LF).

Index	Optimal cutoff value	Sensitivity (%)	Specificity (%)	AUC 95% CI	P	Yorden Index
MELD scores	0.37	73.33	75.56	0.78 (0.67–0.89)	<0.0001	0.49
MAIT cells proportion	0.52	73.33	80.00	0.83 (0.73–0.92)	<0.0001	0.53
Combined detection	0.42	83.33	86.67	0.91 (0.84–0.97)	<0.0001	0.70

larger than that for the MELD score, indicating that the MAIT cell proportion had a higher value than the MELD score in predicting the outcomes of patients with LF. More importantly, the combination of MAIT cell proportion and MELD score can better predict the long-term prognosis of LF patients than any single index, which inspired us to build a combined optimization model that including MAIT cell to better predict the long-term outcome of LF patients in the future. Logistic regression analysis showed that the circulating MAIT cell proportion was an independent risk factor for death in patients with LF. This was a retrospective study with a small sample size, which had certain limitations. Prospective studies with large sample sizes are needed to verify these indicators.

In conclusion, the circulating proportion of MAIT cells decreased in patients with LF but was not dependent on the cause of LF. More importantly, the proportion of MAIT cells is an independent risk factor for death in patients with LF. Finally, we found that the proportion of MAIT cells combined with the MELD score is an outstanding biomarker for long-term prognosis in patients with LF. In the future, multicenter studies with larger sample sizes are required to confirm these findings.

Table 3

Univariate analysis of risk factors for failure (LF).

Variables	95% Confidence interval	*P*
MAIT cells' proportion	0.209–0.782	0.007
Gender	0.558–3.826	0.440
Age	1.001–1.093	0.047
ALT	0.999–1.001	0.782
AST	0.999–1.001	0.495
Total bilirubin	0.999–1.006	0.189
Albumin	0.818–1.029	0.140
Cholinesterase	0.999–1.000	0.048
Prealbumin	0.998–1.011	0.149
Leukocyte count	0.937–1.191	0.368
Neutrophil count	0.986–1.026	0.560
Blood platelet	0.990–1.006	0.586
Prothrombin activity	0.850–0.964	0.002
Creatinine	1.002–1.047	0.032
C-reactive protein	0.994–1.052	0.120
proealcitonin	0.863–3.260	0.128
AFP	1.000–1.001	0.238
MELD score	1.087–1.376	0.001

Abbreviations: AFP = alpha-fetoprotein, ALT = Alanine aminotransferase, AST = Aspartate aminotransaminase, LF = liver failure, MAIT = mucosal-associated invariant T, MELD = models for end-stage liver disease.

Table 4

Multivariate analysis of risk factors for LF patients.

Variables	95% Confidence interval	*P*
MAIT cells proportion	0.000–0.413	0.017
Gender	0.000–2.447	0.105
Age	0.988–1.328	0.071
ALT	0.987–1.002	0.139
AST	0.999–1.018	0.065
Total bilirubin	0.994–1.076	0.093
Albumin	0.599–1.253	0.446
Prealbumin	0.974–1.017	0.651
Cholinesterase	0.999–1.001	0.894
Prothrombin activity	0.171–1.092	0.076
Leukocyte count	0.887–3.447	0.107
Neutrophil count	0.792–1.005	0.061
Blood platelet	0.978–1.021	0.949
Creatinine	0.981–2.112	0.063
C-reactive protein	0.781–1.073	0.276
proealcitonin	0.005–8.629	0.406
AFP	0.998–1.001	0.607
MELD score	0.017–1.391	0.096

Abbreviations: AFP = alpha-fetoprotein, ALT = Alanine aminotransferase, AST = Aspartate aminotransaminase, LF = liver failure, MAIT = mucosal-associated invariant T, MELD = models for end-stage liver disease.

Author contributions

Cheng TC and Li H contributed equally to this work, Cheng TC and Li H performed the experiments and wrote the manuscript, Liu YC, Xue H, and Tian LJ performed the statistical analysis, Bian ZL and Cheng FL designed the study and revised the manuscript.

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