Usefulness of the modified hemophagocytic syndrome diagnostic score as a prognostic factor in lung transplantation patients

Ji Yeon Choi
Yonsei University College of Medicine
Song Yee Kim
Yonsei University College of Medicine
Sang Hoon Lee
Yonsei University College of Medicine
A La Woo
Yonsei University College of Medicine
Seung Hyun Young
Yonsei University College of Medicine
Ah Young Leem
Yonsei University College of Medicine
Eun Young Kim
Yonsei University College of Medicine
Kyung Soo Chung
Yonsei University College of Medicine
Ji Ye Jung
Yonsei University College of Medicine
Young Ae Kang
Yonsei University College of Medicine
Young Sam Kim
Yonsei University College of Medicine
Jin Gu Lee
Yonsei University College of Medicine
Hyo Chae Paik
Yonsei University College of Medicine
Moo Suk Park (pms70@yuhs.ac)
Yonsei University College of Medicine

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Abstract

Background: Lung transplantation (LTX) is an established treatment for end-stage lung disease; however, the post-LTX mortality rate remains high. This study aimed to evaluate the prognostic value of the modified reactive hemophagocytic syndrome diagnostic score (mHScore) and its individual components on mortality after LTX.

Methods: We retrospectively analyzed 294 patients who underwent LTX at Severance Hospital, Yonsei University, Korea, from January 2012 and December 2020, and classified them into high (n=114, mHScore > 104.0) and low mHScore (n=180, mHScore ≤ 104.0) groups. Triglyceride, ferritin, serum glutamic oxaloacetic transaminase, fibrinogen, and cytopenia were used to calculate the mHScore. We compared baseline characteristics and mortality rates as LTX prognostic factors.

Results: The high mHScore group had significantly more cytopenia and higher ferritin, triglyceride, lactate dehydrogenase, and C-reactive protein levels than the low mHScore group. The mortality rate was significantly higher in the high than in the low mHScore group (hazard ratio, 4.429, $p < 0.001$). Multivariate regression analysis revealed that a high mHScore was significantly associated with postoperative mortality, even after adjusting for other confounding factors. A high mHScore was also associated with postoperative complications.

Conclusions: The mHScore can be used to estimate post-LTX prognosis and predict postoperative mortality.

Background

Lung transplantation (LTX) is the most effective therapeutic option for patients with end-stage lung disease [1, 2]. Although the introduction of more effective immunosuppression regimens, advancements in surgical techniques, improved management of postoperative and infectious complications, and adoption of evidence-based guidelines for donor and recipient selection have led to improved outcomes after LTX, the outcomes for LTX remain suboptimal compared to those of other solid-organ transplants[3-7]. Various factors have been evaluated for predicting prognosis in patients who have undergone LTX, including age, underlying disease, bilateral LTX, body mass index (BMI), and malnutrition [8-11]. The immune system plays a critical role in prognosis at all time-points after LTX, because the degree of immunosuppression may increase the risk of infection, malignancy, and rejection [12, 13].

Infection and allograft failure due to primary graft dysfunction (PGD) are the leading causes of death early after LTX, and chronic lung allograft dysfunction is the primary cause of death beyond the first year after LTX. These postoperative complications are generally associated with the immune system, inflammatory processes, and recurrent infections, and directly increase the risk of death [12]. Indeed, the inability to accurately monitor the immune status in immunocompromised patients to predict prognosis remains a significant challenge in clinical practice.

The hyperinflammatory condition caused by infection, malignancy, autoimmune disorders, immunocompromised states, and solid organ transplant may be related to dysregulated and ineffective immune responses and may be a leading cause of poor prognosis. Numerous indicators have been used as markers reflecting immune status, including serum C-reactive protein (CRP), procalcitonin, lactate dehydrogenase (LDH), ferritin, fibrinogen, triglycerides (TG), cytopenia, and cytokines [14-16]. However, there are limits to using these biomarkers independently to predict immune system abnormalities and patient prognosis after LTX. Additionally, although biomarkers have been used to predict infection, there have been no reports on post-LTX survival outcomes according to biomarkers. If prognosis can be predicted using a scoring system that includes individual biomarkers, this may lead to earlier diagnosis of complications during the LTX follow-up period and post-LTX better outcomes.

Fardet *et al*. constructed and validated the HScore for diagnosis of reactive hemophagocytic syndrome, which is a hyperinflammatory condition caused by highly stimulated, but dysregulated and often ineffective immune responses [17]. The HScore is determined by biological (i.e., TG, ferritin, serum glutamic oxaloacetic transaminase [SGOT], fibrinogen levels, and cytopenia), cytological (i.e., hemophagocytosis features in aspirated bone marrow), and clinical (i.e., known underlying immunosuppression, high temperature, and organomegaly) features. Such a hyperinflammatory assessment tool may provide prognostic indicators for patients who have undergone LTX.

In the current study, we investigated whether the postoperative prognosis of LTX patients could be predicted using a modified HScore (mHScore), calculated using only the five biological features (e.g., cytopenia, ferritin, fibrinogen, TG, and SGOT) in peripheral blood. Considering the relationship between a prolonged hyper-inflammatory status and the prognosis of LTX patients, we hypothesized that a high mHScore after LTX may be associated with poor prognosis.

Methods

Study Population and Data Source

This study included 294 patients who underwent LTX at Severance Hospital, Yonsei University, Korea, between January 2012 and December 2020. We retrospectively reviewed the medical data of all patients and extracted information pertaining to demographic characteristics and pre- and postoperative parameters to evaluate the relationships between these variables and survival after LTX. The included patients were divided into low and high mHScore groups, based on their mHScore calculated from 3-month post-LTX laboratory data. We analyzed the following pre-LTX variables: demographic data, including age, sex, and BMI; comorbidities, such as diabetes mellitus and hypertension; primary lung disease; preoperative mechanical ventilation and extracorporeal membrane oxygenation (ECMO); donor–recipient total lung capacity (TLC) ratio, and the ratio of arterial oxygen concentration to the fraction of inspired oxygen (P/F) in the donor.

Modified Hemophagocytic Syndrome Diagnostic Score as a Prognostic Factor

In this study, the mHScore was used to evaluate postoperative prognosis. Five biological variables (i.e., TG, ferritin, SGOT, fibrinogen levels, and cytopenia) were used to calculate the mHScore, using the scoring system at http://saintantonie,aphp.fr/score/. Supplemental Table 1 shows the parameters and criteria for scoring the mHScore. An optimal mHScore cut-off value of 104 for predicting postoperative overall survival was determined using receiver operating characteristic (ROC) curve analysis. When we analyzed serial mHScores (before LTX and 1, 3, 6, and 12 months after LTX), the mHScore at 3 months post-LTX was identified as most appropriate (Figure 1). Consequently, the two groups were classified by an mHScore > 104 (high mHScore) and ≤ 104 (low mHScore) at 3 months after LTX.

Postoperative Complications

We compared the incidence of postoperative complications between patients with low and high mHScores. Acute kidney injury was defined as an increase in the creatinine level to 0.3 mg/dL within 48 hours, or an increase in the creatinine level by 30% from the baseline value during the first 3 months after LTX [18]. Pneumonia was diagnosed according to positive sputum cultures or bronchioalveolar lavage cultures, with corresponding radiological findings, requiring treatment. Any positive blood culture and qSOFA score of ≥ 2 was defined as sepsis. Hemophagocytic lymphohistiocytosis (HLH) was diagnosed if at least five of the eight following features were present: fever, splenomegaly, cytopenia, hypertriglyceridemia, hypofibrinogenemia, evidence of hemophagocytosis in bone marrow aspirates, hyperferritinemia, low natural killer cell activity, or elevated soluble CD25 [19]. Thrombotic thrombocytopenic purpura was defined by the presence of hemolysis, such as thrombocytopenia, anemia, elevated reticulocyte count, elevated serum LDH, and bilirubin levels, fragmented red blood cells on the blood smear, negative direct antiglobulin test, normal coagulation profile, and ADAMTS 13 < 10%, requiring treatment [20, 21]. Hemolytic uremic syndrome was defined by the presence of microangiopahtic hemolytic anemia, thrombocytopenia, and acute renal dysfunction [22]. PGD was graded based on the criteria from the International Society for Heart and Lung Transplantation which is in turnbased on the partial pressure of oxygen/fraction of inspired oxygen ratio and the presence of diffuse parenchymal infiltrates in the allograft on a chest radiograph [23-25]. Acute rejection was defined as a medical condition with clinical evidence of suspected rejection or pathological findings that necessitated steroid pulse therapy. All major postoperative complications and infections during the follow-up period were analyzed.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics software (version 25.0; IBM Corp., Armonk, NY). Data are expressed as means and standard deviations or medians and interquartile ranges, as appropriate. Continuous and categorical variables were analyzed by Student's *t* test and the chi-squared or Fisher's exact test, respectively. The optimal cut-off mHScore was determined using ROC curve analysis. A multivariate logistic regression analysis was performed with variables with $p < 0.05$ in the bivariate analysis to identify independent risk factors. Hazard ratio (HRs) and 95% confidence intervals (CIs) were calculated. Survival data were estimated using the Kaplan—Meier method, and statistical

differences in survival were determined using the log rank test. In all analyses, statistical significance was set at $p < 0.05$.

Results

Cut-off Level of mHScore and Baseline Characteristics

The ROC curves for the mHScore at various perioperative times for prediction of post-LTX prognosis are shown in Figure 1. The median cut-off level of mHScore for the prediction of postoperative prognosis based on the 3-months post-LTX data was 104.0 (area under the curve = 0.71; 95% CI: 0.645–0.779; $p < 0.001$; Fig. 1) and the cut-off level at 3, 6, and 12-months were similar. This cut-off value corresponded to a sensitivity of 65.2% and specificity of 75.3%. Based on this cut-off value, 180 (61.2%) and 114 (38.8%) patients were classified into the low mHScore (≦104.0) and high mHScore (> 104.0) groups, respectively.

The baseline characteristics of all patients who underwent LTX are shown in Table 1. The most common reason for LTX was idiopathic pulmonary fibrosis in both groups. There was no significant difference between low and high HScore groups in the following preoperative parameters: age, sex, BMI, comorbidities, primary lung disease, preoperative mechanical ventilation, preoperative ECMO, donor–recipient TLC ratio, and donor P/F ratio. Table 2 presents the explanatory variables of inflammatory marker levels in LTX patients categorized by mHScore. LDH and CRP levels were significantly higher in the high than in the low mHScore group.

Table 1. Basal characteristics of patients classified by mHScore after lung transplantation.

Variables	Total (n = 294)	Low mHScore (n = 180)	High mHScore (n = 114)	*p*-value
Age, years	53.8 ± 12.5	52.7 ± 12.2	55.5 ± 12.7	0.058
Male sex, n (%)	141 (48.0)	84 (46.7)	57 (50.0)	0.331
Body mass index, kg/m^2	20.9 ± 4.1	21.0 ± 3.7	20.8 ± 4.6	0.658
Comorbidity				
Hypertension, n (%)	67 (22.8)	46 (25.6)	21 (18.4)	0.248
Diabetes mellitus, n (%)	80 (27.2)	48 (26.7)	32 (28.1)	0.683
Primary lung disease				
IPF, n (%)	153 (52.0)	96 (53.3)	57 (50.0)	0.632
CTD ILD, n (%)	50 (17.0)	30 (16.7)	20 (17.5)	0.874
BE, n (%)	18 (6.1)	113 (62.8)	5 (4.4)	0.455
LAM, n (%)	5 (1.7)	3 (1.7)	2 (1.8)	1.000
COPD, n (%)	11 (3.7)	8 (4.4)	3 (2.6)	0.538
BO after PBSCT, n (%)	23 (7.8)	12 (6.7)	11 (9.6)	0.378
Others*, n (%)	34 (11.6)	18 (10.0)	16 (14.0)	0.350
Preoperative MV, n (%)	106 (36.1)	67 (37.2)	39 (34.2)	1.000
Preoperative ECMO, n (%)	88 (29.9)	59 (32.8)	29 (25.4)	0.353
Donor-recipient TLC ratio	107.3 ± 18.8	107.9 ± 18.1	106.2 ± 19.9	0.478
Donor P/F ratio	455.6 ± 92.5	462.3 ± 92.2	444.8 ± 92.5	0.126

Values are expressed as means (standard deviations) or median (interquartile ranges).

mHScore, modified hemophagocytic syndrome score; IPF, idiopathic pulmonary fibrosis; CTD ILD, connective tissue disease interstitial lung disease; BE, bronchiectasis; LAM, lymphangioleiomyomatosis; COPD, chronic obstructive pulmonary disease; BO after PBSCT, bronchiolitis obliterans after peripheral blood stem cell transplantation; MV, mechanical ventilation; ECMO, extracorporeal membrane oxygenation; TLC, total lung capacity; P/F, ratio of arterial oxygen concentration to the fraction of inspired oxygen. *'Others' include non-specific interstitial pneumonia, pleuroparenchymal fibroelastosis, acute respiratory distress syndrome, and acute fibrinous and organizing pneumonia.

Table 2. Assessment of variables in patients classified by mHScore after lung transplantation.

	Low mHScore (n = 180)	High mHScore (n = 114)	*p* value
Leukocyte count, 10^6 /liter	6.6 (4.3)	6.2 (4.6)	0.327
Hemoglobin, gm/dl	11.2 (1.9)	9.6 (2.0)	0.675
Platelets, 10^9 /liter	239.7 (105.6)	153.5 (106.5)	0.809
Ferritin, ng/ml	618.6 (1099.7)	3296.6 (6680.1)	<0.001
LDH, IU/liter	361.5 (164.6)	626.2 (814.7)	<0.001
Triglycerides, mmoles/liter	167.45 (95.9)	225.9 (157.1)	<0.001
SGOT, IU/liter	88.1 (523.9)	298.4 (1018.5)	<0.001
SGPT, IU/liter	35.8 (101.9)	64.0 (154.9)	0.027
Fibrinogen, mg/dl	300.6 (119.5)	314.9 (140.8)	0.072
CRP, mg/L	19.9 (54.0)	46.0 (666.7)	0.001

Values are expressed as means (standard deviations). mHScore, modified hemophagocytic syndrome score; LDH, lactate dehydrogenase; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; CRP, C-reactive protein.

Relationship between Postoperative mHScore and Postoperative Overall Survival

Univariate analysis revealed that age, BMI, high mHScore, donor P/F ratio, LDH, and CRP level were independent prognostic factors for post-LTX survival (Table 3). Multivariate logistic regression analysis was performed using factors that achieved $p < 0.05$ in the bivariate analysis. The HR was 3.013 (95% CI: 1.451–6.257; $p = 0.003$) for a high mHScore. Other independent risk factors for postoperative prognosis were age (HR 1.037, 95% CI: 1.001–1.074, $p = 0.044$), BMI (HR 1.130, 95% CI: 1.026–1.245, $p = 0.013$), donor P/F ratio (HR 0.995, 95% CI: 0.991–0.999 $p = 0.010$), LDH (HR 1.004, 95% CI: 1.001–1.006, $p = 0.002$), and CRP level (HR 1.038, 95% CI: 1.020–1.056, $p < 0.001$).

The Kaplan–Meier plots for the low and high mHScore groups are shown in Figure 2. The overall survival rate was significantly higher in the high mHScore group than in the low mHScore group (log-rank test; $p < 0.001$).

Table 3. Univariate and multivariate regression analysis of the association between various parameters and survival after lung transplantation.

	Univariate analysis		Multivariate analysis*	
Variables	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age, years	1.053 (1.027-1.081)	<0.001	1.037 (1.001-1.074)	0.044
Male sex	1.131 (0.683-1.872)	0.632		
Body mass index, kg/m^2	1.123 (1.052-1.200)	0.000	1.130 (1.026-1.245)	0.013
Comorbidity				
Hypertension	1.098 (0.624-1.931)	0.747		
Diabetes mellitus	1.101 (0.645-1.877)	0.725		
Primary lung disease				
IPF	1.274 (0.781-2.076)	0.332		
CTD ILD	1.046 (0.556-1.964)	0.890		
BE	0.463 (0.148-1.446)	0.185		
LAM	0.000 (0.000-0.000)	0.999		
COPD	1.133 (0.312-4.113)	0.849		
BO after PBSCT	0.344 (0.096-1.226)	0.100		
Others	1.670 (0.771-3.616)	0.194		
mHScore				
Low mHScore (<104)				
High mHScore (≥104)	4.429 (2.634-7.445)	0.000	3.013 (1.451-6.257)	0.003
Preoperative MV, n (%)	1.368 (0.823-2.273)	0.226		
Preoperative ECMO, n (%)	1.060 (0.623-1.801)	0.830		
Donor-recipient TLC	1.006 (0.993-1.019)	0.368		
Donor P/F ratio	0.995 (0.992-0.998)	<0.001	0.995 (0.991-0.999)	0.010
Leukocyte count, 10^6 /liter	1.105 (1.040-1.174)	0.001		
Hemoglobin, gm/dl	0.601 (0.514-0.703)	<0.001		
Platelets, 10^3 /liter	0.991 (0.988-0.994)	<0.001		
Ferritin, ng/ml	1.001 (1.001-1.001)	<0.001		
Fibrinogen, mg/dl	1.001 (0.999-1.003)	0.357		
Triglycerides, mmoles/liter	1.002 (1.000-1.004)	0.059		

SGOT, IU/liter	1.025 (1.012-1.037)	<0.001		
LDH	1.006 (1.004-1.007)	<0.001	1.004 (1.001-1.006)	0.002
CRP, mg/L	1.044 (1.028-1.060)	<0.001	1.038 (1.020-1.056)	<0.001

HR, hazard ratio; CI, confidence interval; mHScore, modified hemophagocytic syndrome score; IPF, idiopathic pulmonary fibrosis; CTD ILD, connective tissue disease interstitial lung disease; BE, bronchiectasis; LAM, lymphangioleiomyomatosis; COPD, chronic obstructive pulmonary disease; BO after PBSCT, bronchiolitis obliterans after peripheral blood stem cell transplantation; MV, mechanical ventilation; ECMO, extracorporeal membrane oxygenation; TLC, total lung capacity; P/F, ratio of arterial oxygen concentration to the fraction of inspired oxygen; SGOT, serum glutamic oxaloacetic transaminase; LDH, lactate dehydrogenase; CRP, C-reactive protein. *The multivariable logistic regression model was done by adjusting for age, sex, BMI, P/F ratio, LDH, and CRP.

Relationship between Postoperative mHScore and Causative Postoperative Complications

We also analyzed the correlation between the mHScore and the incidence of postoperative complications (Table 4). The proportions of patients requiring renal replacement therapy and with postoperative bleeding were significantly higher for the high mHScore group than in the low mHScore group (64.9% vs. 30.0%, $p < 0.001$; 27.4% vs. 8.9%, $p < 0.001$, respectively). The incidence of PGD ≥ grade 3 was significantly higher in the high mHScore group than in the low mHScore group (59.6% vs. 46.7%, $p = 0.032$). Although not statistically significant, the incidence of acute rejection was higher in the high mHScore group (7.9% vs. 2.8%, $p = 0.053$). In addition, the duration of intensive care unit admission after LTX and the duration of time on ECMO after LTX were significantly longer in the high mHScore group than the low mHScore group.

Table 4. Causative postoperative complications in patients classified by mHScore after lung transplantation.

Characteristics	Total (n = 294)	Low mHScore (n = 180)	High mHScore (n = 114)	*p*-value
AKI, n (%)	73 (24.8)	39 (21.7)	34 (29.8)	0.181
RRT, n (%)	128 (42.4)	54 (30.0)	74 (64.9)	<0.001
Pneumonia, n (%)	69 (23.5)	47 (26.1)	22 (19.3)	0.205
Sepsis, n (%)	33 (11.2)	19 (10.6)	14 (12.3)	0.706
TTP, n (%)	16 (5.4)	8 (4.4)	8 (7.0)	0.430
HUS, n (%)	6 (2.0)	3 (1.7)	3 (2.6)	0.680
HLH, n (%)	8 (2.7)	3 (1.7)	5 (4.4)	0.268
BPF, n (%)	19 (6.5)	9 (5.0)	10 (8.8)	0.228
Bronchial stenosis, n (%)	41 (13.9)	24 (13.3)	17 (14.9)	0.732
Postoperative bleeding, n (%)	47 (16.0)	16 (8.9)	31 (27.4)	<0.001
GI bleeding, n (%)	23 (7.8)	16 (8.9)	7 (6.1)	0.505
Acute rejection	14 (4.8)	5 (2.8)	9 (7.9)	0.053
Grade 3 PGD, n (%)	152 (51.7)	84 (46.7)	68 (59.6)	0.032
Postoperative ICU LOS, days	16.1 (24.0)	13.1 (15.5)	21.0 (33.0)	0.004
Postoperative ECMO, days	5.0 (30.7)	1.7 (2.5)	10.4 (49.6)	<0.001

Values are expressed as means (standard deviations). mHScore, modified hemophagocytic syndrome score; AKI, acute kidney injury; RRT, renal replacement therapy; TTP, thrombotic thrombocytopenic purpura; HUS, hemolytic uremic syndrome; HLH, hemophagocytic lymphohistiocytosis; BPF, bronchopleural fistula; GI, gastrointestinal; PGD, primary graft dysfunction; LOS, length of stay; ICU, intensive care unit; ECMO, extracorporeal membrane oxygenation.

Discussion

In the present study, we investigated the association between postoperative mHScore and LTX prognosis, including overall survival and complications among LTX recipients. We showed that mortality and postoperative complication rates were higher in patients with a high mHScore, even after adjusting for other confounding factors. These findings suggest that a high mHScore is an independent predictor of a poor survival rate among patients undergoing LTX.

The survival and quality of life post-LTX has increased as the technique has advanced, and the median survival time in the most recent era (2009–2016) is 6.5 years [6]. However, the rate of postoperative mortality remains high as compared with that of other types of solid organ transplants [5, 6, 26].

According to previous reports of adult LTX recipients from 1990 through 2017, infection and graft failure are the leading causes of death in the first post-transplant years, compared to bronchiolitis obliterans syndrome, graft failure, malignancy, and infection in later years [6]. According to the ISHLT Registry, infection remains a significant problem at all time-points after LTX. Efforts have been made to analyze and address perioperative risk factors to improve the survival rate after lung transplantation. Accordingly, various factors have been proposed for evaluating the prognosis of patients undergoing LTX, including donor/recipient age, underlying disease, operative factors, and malnutrition [6, 9-11]. However, no previous study has reported the association of biomarkers with post-LTX prognosis. Our study suggests that a high HScore is an independent predictor of overall survival in LTX recipients. To the best of our knowledge, no previous study has evaluated the association between high inflammation status (as assessed using the mHScore) and survival in LTX recipients.

The mHScore is based on five biological features: cytopenia, ferritin, fibrinogen, triglyceride, and SGOT levels. The HScore was originally developed to diagnose HLH, and includes one cytological and three clinical features, in addition to the five biological features. In this study, we modified the score to represent high inflammatory status in LTX patients, by using only the laboratory values that can be easily measured.

Cytopenia, including leukopenia, anemia, and thrombocytopenia, occurs after a solid organ transplant. The etiology of cytopenia is multifactorial and includes drugs, infections, and post-transplant lymphoproliferative disorders [27]. It also increases the risk of developing further complications, such as opportunistic infections, and may contribute to poor prognosis in patients undergoing LTX. Several studies have reported that leukopenia is associated with decreased survival and increased rates of infection in LTX recipients [28, 29].

Iron metabolism is intrinsically linked to innate immunity by regulation of iron availability to pathogens. A high iron status is related to many infectious diseases and inflammatory responses [15]. Maher *et al*. suggested that an excess of iron stored in ferritin may increase the risk of exposure to iron radicals, reactive oxygen species, and subsequent fibrosis, leading to a poor prognosis [30].

Plasma fibrinogen is an acute phase protein that increases with inflammation or tissue necrosis. It is also related to coagulopathy, which may decrease in response to infection, massive blood loss, and to a dilution effect caused by fluid replacement. Coagulation disorders are common in HLH patients, and several retrospective studies have reported their prognostic role in adult HLH [31, 32]. Fibrinogen, as a risk factor for bleeding complications in LTX patients, has been reported in a retrospective cohort study. It is also a biomarker of disseminated intravascular coagulation [33].

Lipid abnormality, including hypertriglyceridemia, is caused by high levels of inflammatory cytokines resulting from a dysregulated immune system [34, 35].

An abnormal liver function was used a marker of acute liver failure in this study. LDH can act as a prognostic marker of diseases, including hemolytic anemia and infections. In our study, LDH and CRP

levels, which were not included as components of the mHScore, correlated with overall survival in patients undergoing LTX.

Each of these values is an indicator of infection and a dysregulated immune response in immunocompromised patients. This study is meaningful in revealing biomarkers that correlated with poor prognosis post-LTX.

Nevertheless, this study had several limitations worth noting. First, it represents the clinical experience from a single center. Second, this study had a retrospective design, with the possibility of bias in the selection of parameters. Third, the HScore is a scoring system originally developed for the diagnosis of HLH, and we applied a subsection of this score in LTX recipients, without validation of its utility in this patient population; therefore, we cannot exclude the possibility that the weight of the score was over- or under-applied in this population. However, the strength of this study is that it showed the predictive value of the mHScore and its component biomarkers in LTX patients. In the future, we will construct a prognostic scoring model specifically for LTX patients using the inflammatory markers included in the mHScore.

Conclusion

The current results showed that overall survival was significantly longer for the high mHScore group than for the low mHScore group. These findings suggest that the mHScore is a useful marker for predicting prognosis in post-LTX patients. By alerting clinicians to the patient's likely prognosis, this finding may facilitate the development of both preventive and early intervention strategies that can improve the overall survival of LTX patients.

Abbreviations

CI, confidence interval

CRP, C-reactive protein

ECMO, extracorporeal membrane oxygenation

HLH, hemophagocytic lymphohistiocytosis

HR, hazard ratio

LDH, lactate dehydrogenase

LTX, lung transplantation

mHScore, modified reactive hemophagocytic syndrome diagnostic score

P/F, ratio of arterial oxygen concentration to the fraction of inspired oxygen

PGD, primary graft dysfunction

SGOT, serum glutamic oxaloacetic transaminase

TLC, total lung capacity

Declarations

Ethics approval and consent to participate

This research protocol was approved by the institutional review board of Severance Hospital, South Korea (IRB No. 4-2021-0264) and study design was approved by the appropriate ethics review boards. The requirement to obtain informed patient consent was waived due to the nature of the study.

Consent for publication

Not applicable.

Availability of data and materials

Individual participant data will not be made available.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

J.Y.C was involed in the original conception and design of the work and wrote the paper. S.Y.K, S.H.L, A.L.W, S.H.Y, A.Y.L, E.Y.K, K.S.C, J.Y.J, Y.A.K, Y.S.K, J.G.L, and H.C.P drafted and revised the manuscript. M.S.P designed the concept and finally approved the paper. All authors have taken due care to ensure the integrity of this work. The final manuscript has been read and approved by all authors.

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Figures

Figure 1

Receiver operating characteristic curve analysis for determining the cut-off value of the modified hemophagocytic syndrome score (mHScore) that best predicts overall survival in lung transplantation (LTX) patients. The optimal cut-off value for the mHScore is 104 (area under the curve [AUC] = 0.71; 95% confidence interval [CI], 0.645–0.779; p < 0.001) at 3 months after LTX. The cut-off value was 56.5 (AUC = 0.52; 95%CI, 0.441–0.589; p = 0.687) preoperatively, 32.5 (AUC = 0.63; 95%CI, 0.557–0.698; p-value = 0.001) at 7 days (7D), 64.5 (AUC = 0.58; 95%CI, 0.504–0.651; p = 0.038) at 1 month (1M), 103.5 (AUC = 0.77; 95%CI, 0.708–0.833; p < 0.001) at 6 months (6M), 103.5 (AUC = 0.84; 95%CI, 0.785–0.897; p < 0.001) at 12 months (12M) respectively.

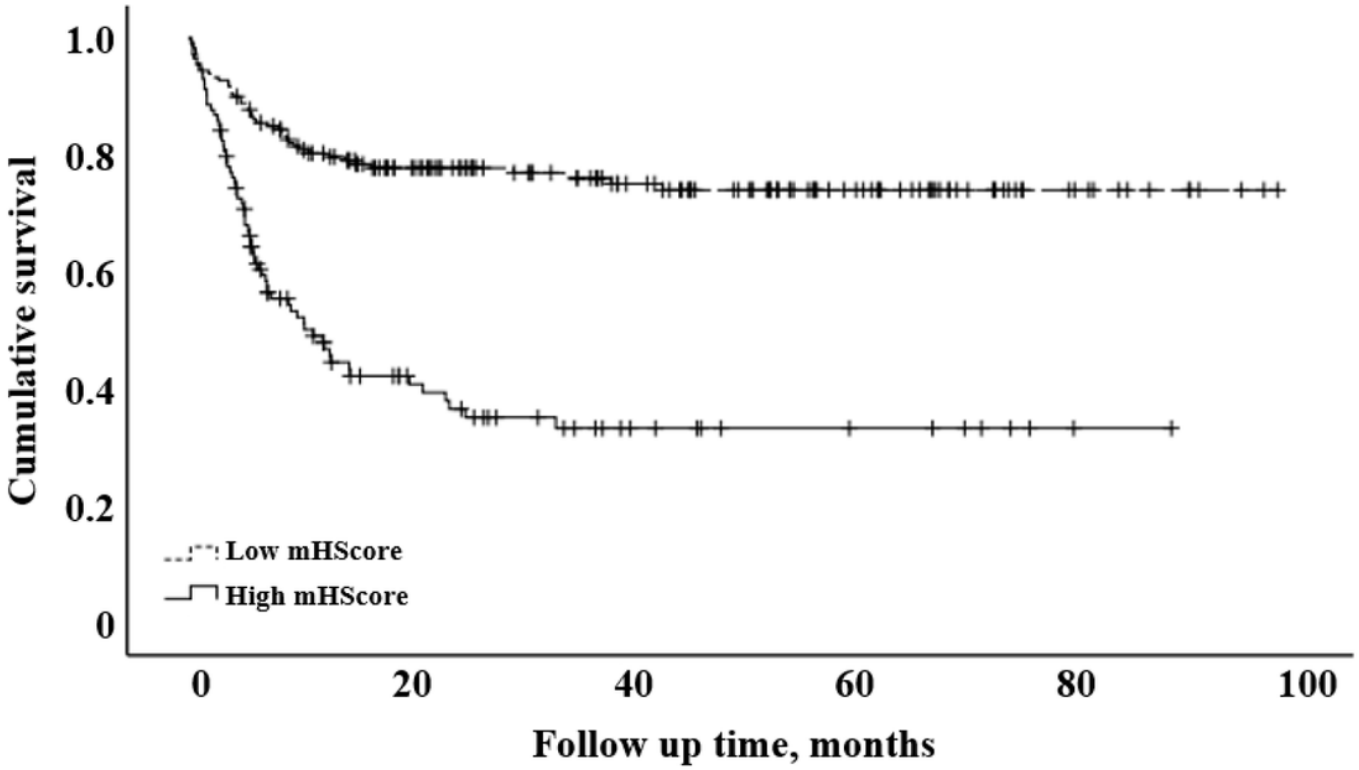

Figure 2

Figure 2

Kaplan–Meier survival curve after lung transplantation according to the modified hemophagocytic syndrome score (mHScore) at 3 months postoperatively. High mHScore group was significantly associated with poor survival (Log-Rank $p < 0.001$).

Supplementary Files

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