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Individual mHLA-DR trajectories in the ICU as predictors of early infections following liver transplantation: a prospective observational study

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Abstract

Background Infections are a leading cause of early mortality after liver transplantation (LT). Prior to transplantation, cirrhosis-associated immune dysfunction significantly increases the risk of infection. This study investigated the potential of immune monitoring, with a focus on monocytic HLA-DR (mHLA-DR) expression, as a predictor of post-LT complications.

Methods We conducted a prospective study on 130 patients awaiting LT at Lyon University Hospital to assess mHLA-DR expression, lymphocyte subsets, and T-cell function before and after LT. Multivariate analysis and K-means longitudinal clustering were performed to explore the relationships between immune trajectories and clinical outcomes.

Results Among the 99 patients who underwent LT, 35.4% experienced infections early post-LT. No difference in outcome was found regarding lymphocyte count or function. Delayed mHLA-DR recovery (Day 7 < 11,000 AB/C) and pre-LT MELD scores > 30 emerged as independent infection risk factors, with ORs of 12.1 [4.4–38.2], $p < 0.0001$ and 4.9 [1.4–18.4], $p = 0.01$, respectively. Patients with delayed mHLA-DR restoration also had reduced one-year survival (77.8% versus 98.3%, $p = 0.003$). K-means clustering revealed three distinct mHLA-DR recovery profiles, with the slowest recovery group showing the poorest outcomes.

Conclusions Our findings highlight mHLA-DR as an early predictor of post-LT infections. Monitoring post-LT immune function through mHLA-DR expression could guide individualized management strategies to improve outcomes.

Trial registration The study was registered in the ClinicalTrials.gov registry: NCT03995537, date: June 20, 2019.

Keywords Liver transplantation, MHLA-DR, Immune dysfunction, Infections, Immune monitoring, Transplant outcomes, ICU

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Background

Liver transplantation (LT) is a cornerstone treatment for patients with end-stage liver diseases, offering significant improvements in survival and quality of life. Over the past three decades, survival rates after LT have markedly increased. However, infections continue to be a major complication in the posttransplant period and remain the leading cause of early mortality and morbidity despite advances in surgical techniques, immunosuppressive drugs and infection control strategies [1]. Notably, infections are critical issues within the first 3 months after LT, accounting for 33–51% of deaths according to pre-LT disease severity [1]. Consequently, effective monitoring and assessment of the risk of infectious complications remains a critical challenge for providing timely and individualized patient care.

Several risk factors for infections following LT have been identified and are related to pre-LT conditions and surgical complications [2, 3]. However, to date, no data support immune monitoring to assess the risk of post-LT infections. The post-LT prognosis is impaired for patients with pre-LT severe liver disease, especially patients who present with acute-on-chronic liver failure (ACLF) [4, 5]. These patients already present with marked immune alterations known as cirrhosis-associated immune dysfunction (CAID) before LT. Like sepsis, ACLF is characterized by both systemic inflammation and profound immunosuppression, likely as a consequence of alterations in the gut–liver axis, leading to intestinal hyperpermeability and dysbiosis [6, 7]. This results in continuous immune stimulation by microbial antigens, ultimately causing immune cell exhaustion [6]. Consequently, both innate (e.g., increased numbers of immature neutrophils, low expression of HLA-DR on monocytes, altered monocyte release of inflammatory cytokines) and adaptive (e.g., lymphopenia, increased expression of checkpoint inhibitors, altered IFN-γ lymphocyte release) immune responses are impaired in ACLF patients, dramatically increasing their susceptibility to infections [8–11]. While ACLF patients face greater perioperative risks and post-transplant complications, with infections being the predominant cause of death within one year post-LT, the potential impact of immune status before LT on post-LT outcomes (infections, graft rejection, mortality) has yet to be fully explored. This underscores the need for comprehensive studies that include both pre-LT and post-LT assessments to better delineate individualized post-LT management strategies.

In the present work, we leveraged standardized cellular immunology parameters, which are now commonly used in intensive care unit (ICU) patients, to monitor the occurrence of immunosuppression following injuries (sepsis, trauma, surgery) and its association with infections [12, 13]. In a prospective observational monocentric study, we measured monocytic HLA-DR (mHLA-DR) expression, T lymphocyte subsets, and ex vivo IFN-γ release following non-antigen-specific stimulation before and over one month after LT in a cohort of patients receiving the same immunosuppression protocol. The primary objective was to assess whether any immunological parameters are associated with clinical outcomes, such as infections, graft rejection and one year mortality.

Patients and methods

Patients

We conducted an observational, prospective and longitudinal study to assess the kinetics of immune parameters following LT. We consecutively enrolled patients from February 2020 to May 2023 in the EdMonHG study (monocytic expression of HLA-DR after liver transplantation, ClinicalTrials.gov identifier NCT03995537) at Lyon University Hospital (*Hospices Civils de Lyon*). The study was conducted in accordance with the Helsinki Declaration and approved by the *Comité de Protection des Personnes Ile de France* XI (approval number 19039–40433). Written informed consent was obtained from all participants prior to enrollment.

The inclusion criteria included patients awaiting LT, with acute liver failure (ALF), compensated cirrhosis (compensated advanced chronic liver disease [cACLD] with hepatocellular carcinoma [HCC]), or decompensation of cirrhosis, with or without organ failure (decompensated advanced chronic liver disease [dALCD] including nonacute decompensation [N-AD], acute decompensation [AD] and ACLF). Patients receiving immunosuppressive therapy before LT (with the exception of corticosteroids) and patients without underlying liver disease were excluded. Patients awaiting multiorgan transplantation or retransplantation were also not eligible for the study.

Outcome

Postoperative infections were defined according to the American Society of Transplantation [14](Supplementary Data), and only significant infections were recorded (excluding uncomplicated cystitis and catheter colonization).

The diagnosis of acute graft rejection was based on the presence of liver enzyme disturbances and histological criteria, according to the Banff schema for grading liver allograft rejection: an international consensus document, with a Banff score ≥ 4 [15]. Postoperative complications and infections were analysed if they occurred within 1 month post-LT, and survival status was assessed at 1 year post-LT. Finally, patients finished the study 1 year

after inclusion if no liver transplantation occurred at that time.

LT management

Following deceased-donor graft assignment, orthotopic LT was performed according to standard procedures. Immunosuppressive therapy, including basiliximab induction, corticosteroids until day (D)7 and mofetil mycophenolate, was started immediately. Tacrolimus (with a target trough concentration of 8–10 ng/mL) was introduced on D3.

Immunomonitoring

Blood samples were collected before LT (at inclusion and then every 3 months until LT or earlier in case of acute events) and twice a week for 1 month following LT. We analysed mHLA-DR expression, lymphocyte subsets and T-cell function. mHLA-DR expression was measured via flow cytometry in fresh whole blood samples according to a standardized protocol [16]. The results were obtained on a Navios Cytometer (Beckman Coulter, FL) and are expressed as the number of antibodies bound per cell (AB/C). Peripheral blood cell counts were performed to assess total lymphocytes, T-cell counts (CD3) and T-cell subsets (CD4, CD8) via flow cytometry. The cells were analysed on an AQUIOS cytometer (Beckman Coulter, FL) [17]. T-cell function was assessed via a whole-blood interferon-γ release assay (IGRA). This antigen-independent test uses an enzyme-linked immunofluorescence assay (ELFA) to measure IFN-γ production in response to phytohemagglutinin A (PHA) stimulation. The results were obtained on a VIDAS-3 (bioMérieux, Marcy l'Etoile, France) and expressed as a reference fluorescence value (RFV).

Statistics

The results are expressed as medians and interquartile ranges (IQRs) or numbers and percentages (%). Univariate comparisons were performed via the Mann–Whitney U test for two groups, the Kruskal–Wallis test for more than two groups of continuous variables, and the chi–square test or Fisher's exact test for categorical variables.

For post-LT biological data analysis, we censored patients at the time of major immune event occurrence (i.e., treatment of acute cellular rejection or severe infection as defined above).

Backwards stepwise multivariate analysis via a logistic regression model was performed to assess factors that predict post-LT outcomes (infections, acute graft rejection, and one-year mortality). Variables with a p value < 0.10 in the univariate analysis were included in the model. The area under the receiver operating characteristic (ROC) curve was constructed to identify optimal cut-off values for quantitative variables, defined as the value associated with the highest sum of sensitivity and specificity (Youden's index). In cases of collinearity between two variables, we selected the variable that resulted in the lowest Akaike information criterion (AIC) [18] to ensure a better model fit.

To identify patients with common post-LT mHLA-DR kinetics over time (trajectory endotypes), we used KmL—Kmeans for longitudinal data—R package 2.4.1 [19]. The KmL method pipeline involves clustering marker trajectories using the k-means algorithm with a Gower adjusted Euclidean distance metric to handle missing data. For each number of clusters (ranging from 2 to 5), we ran the KmL method a thousand times to select the best clustering partition based on the highest Calinski-Harabasz metric, which compares within-cluster and between-cluster dispersion to evaluate partition quality. Since the Calinski-Harabasz metric is not tolerant of missing values, imputation is needed before its computation. Missing values within each cluster were imputed using linear interpolation to follow the cluster's population mean trajectory shape. After determining the best clustering partition for each number of clusters, we then used the Calinski-Harabasz metric again to select the optimal number of clusters.

Survival curves were generated via Kaplan–Meier estimates, and differences were compared via the log-rank test. R version 4.0.2. (R Core Team 2018, Vienna, Austria) and GraphPad Prism 6.0 (GraphPad Software, La Jolla California, USA) were used for all analyses. The significance level was set at $p < 0.05$.

Results

Patient clinical characteristics

One hundred thirty patients were included. Over the study duration, 100 patients were transplanted: 99 patients underwent LT, and 1 patient underwent liver–kidney transplantation; these patients were excluded from the analyses. Among the 30 remaining patients at 1 year, 15 patients died on the waiting list (WL), 4 were removed from WL due to clinical improvement, and 11 still awaited LT (Fig. 1).

Thirty patients were not transplanted after 1 year from inclusion (15 patients died before LT, 4 were removed from WL for improvement of disease, and 11 still remained on WL), 99 patients underwent liver transplantation, and 1 patient received combined kidney liver transplantation. LT: liver transplantation, WL: waiting list.

LT recipients were mainly male (n = 80, 81%), with a median age of 56 years [48–61]. The median MELD score at LT was 20 [15–29]. dACLD accounted for 74 patients (23 with N-AD, 20 with AD, and 31 with ACLF),

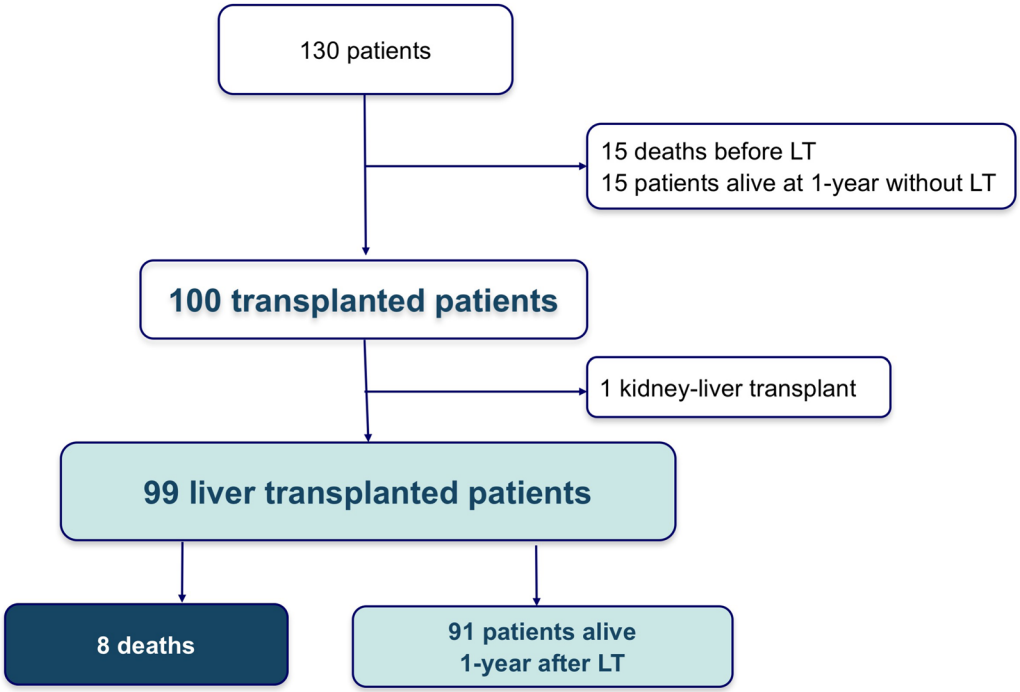

Fig. 1 Flow chart showing outcomes following enrolment in the study

20 patients exhibited cACLD, and 5 patients were admitted for ALF. The most common underlying liver disease in ACLD patients was alcohol-related liver disease (ALD, n = 69, 70%), followed by viral infections (n = 12, 12%), autoimmunity (n = 9, 9%), metabolic dysfunction-associated steatohepatitis (MASH) (n = 3, 3%) and progressive familial intrahepatic cholestasis (n = 1, 1%). ALF etiologies were acute hepatitis B virus infection (n = 2), autoimmune hepatitis (n = 1), post-traumatism ischemia (n = 1) and malignant hyperthermia (n = 1). Among the ACLF patients, the median number of organ failures (OFs) at inclusion was 2 [1–3], 7 (22,6%) patients presented with Grade 1 ACLF, 12 (38,7%) with Grade 2 ACLF and 12 patients (38,7%) with Grade 3 ACLF. With respect to OF, liver failure (20/31), coagulation failure (20/31) and kidney failure (10/31) were the most common. Thirty-four patients were hospitalized when called for LT (22 in the ICU). The donors were mainly men (n = 63, 64%), with a median age of 66 [51–72] years. The main causes of donor death were vascular (n = 49, 50%) and anoxic (n = 31, 31%), followed by trauma (n = 17, 17%). Seventeen grafts were donated after circulatory death (DCD). The median surgery time was 380 [309–458] minutes, and the median cold and warm ischemia times were 395 [328–468] and 37 [27–41] minutes, respectively. Recipients received a median of 3 [0–5] red blood cell units during surgery, and the median lactate peak was 4.3 mmol/l [3.2–7.3]. After LT, 12 patients received corticosteroids longer than one week because of the increased risk of acute graft rejection.

Kinetics of immune parameters before and following LT

Overall, following LT, immune parameters exhibited a similar pattern of evolution. In the first days post-LT, we observed a decrease in all the values compared with both the baseline values and the laboratory reference ranges. mHLA-DR expression then progressively increased until D30, returning above the lower limit of normal values (i.e., over 13,500 AB/C [24]) between D10 and D15 post-LT (Fig. 2A).

The lymphocyte and T-cell counts increased from D1 to D7 but remained below normal values (i.e., under 1000 cells/µl and 595 cells/µl according to laboratory standards, respectively) until D30 (Fig. 2B, C). CD4 and CD8 T cells decreased after LT, reaching the lower limit of normal values (i.e., 336 cells/µl and 125 cells/µl, respectively) from D7–D10 until D30 (Fig. 2D–E). Finally, IFN-γ production levels were profoundly altered on D1 and remained low throughout the follow-up period (Fig. 2F).

Association between immune parameters and clinical outcomes

Association with the occurrence of infections

At least one severe early post-LT infection occurred in 35 patients (35.4%). The median time to diagnosis was 9 [6–14] days. The most frequent infections were

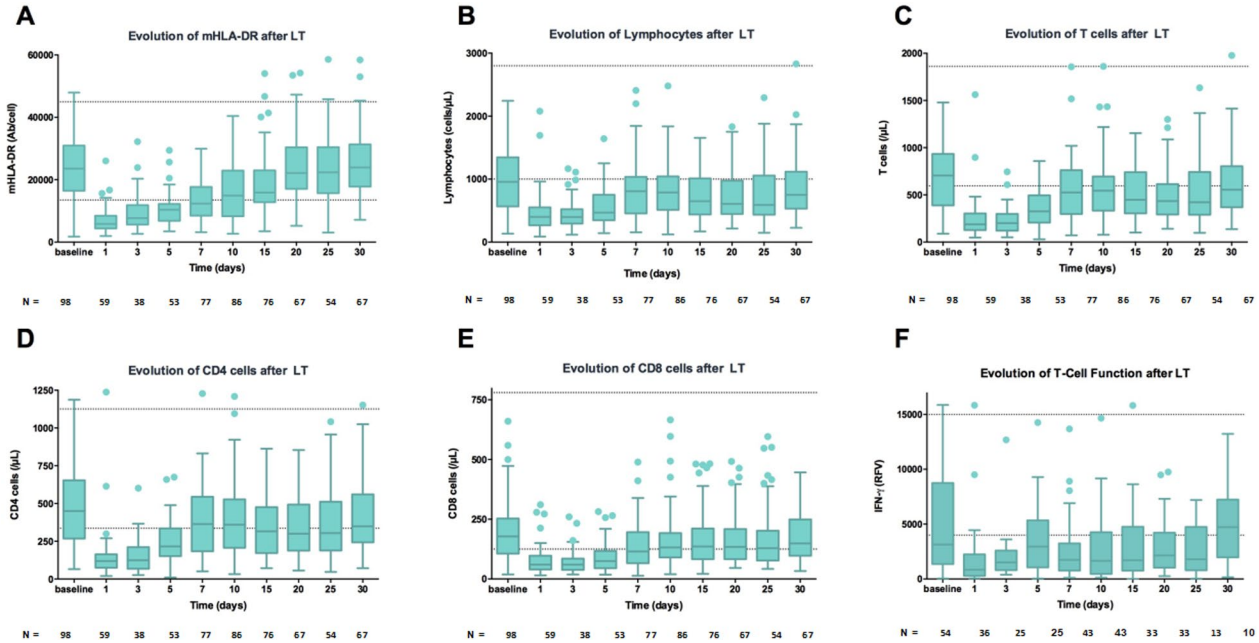

Fig. 2 Evolution of immune markers after liver transplantation (LT). Monocyic expression of HLA-DR expressed as an antibody by cells (**A**), total lymphocytes (**B**), T lymphocytes (**C**), CD4 lymphocytes (**D**), CD8 lymphocytes (**E**) and T lymphocyte function according to the interferon—gamma release assay aftr stimulation, expressed as the reference fluorescence value (**F**). The dotted lines represent the lower and upper limits of normal values previously reported for healthy volunteers. AB/C: antibodies per cell, LT: liver transplantation, mHLA-DR: monocytic HLA-DR, RFV: reference fluorescence value

intra-abdominal infections (n = 19), followed by pneumonia (n = 15) and bacteremia (n = 2). Recipients, donors and transplantation characteristics according to the occurrence of infections are depicted in Table 1.

Infected patients exhibited increased severity of pre-LT liver disease, organ failure at the time of LT and a greater number of RBCs transfused during LT. In terms of immune parameters, the mHLA-DR values were significantly lower from D5 to D15 (Supplementary Table 1, Fig. 3A) in patients who later developed infections.

No other difference in T lymphocyte count or T-cell function was found at any time (Supplementary Table 1, Supplementary Fig. 1).

Since mHLA-DR expression was the only immune parameter that differed between groups (i.e., no infection vs. forthcoming infection), we further assessed its predictive performance for early post-LT infections at each time point where significant differences were observed. On day 7, the area under the curve (AUC, from ROC analysis) was 0.80 (95% CI [0.70–0.90], $p < 0.0001$), with an optimal cut-off value of 11,000 AB/C (Se: 77%, Sp: 76%), as determined by the Youden index. On day 10, the AUC was 0.86 (95% CI [0.73–0.99], $p < 0.0001$), with an optimal cut-off value of 12,000 AB/C (Se: 85%, Sp: 79%). On day 15, the AUC was 0.94 (95% CI [0.88–1.00], $p < 0.0005$), with an optimal cut-off value of 13,000 AB/C (Se: 88%, Sp: 100%). Analyses were not performed for D5 because of the low number of patients. Next, we conducted a multivariate analysis to determine whether mHLA-DR remained an independent predictor of future infection when clinical confounders were included. For this purpose, we included MELD score at LT, number of red blood cell units transfused during LT, baseline mHLA-DR and D7 mHLA-DR levels in the model. The severity of liver disease, presence of organ failure at the time of LT, ACLF Grade and hospitalization status at the time of LT were also tested as alternatives to the MELD score (due to their collinearity) but demonstrated a poorer model fit. We focused on the D7 mHLA-DR value despite the lower AUC because this time point was the most relevant regarding the timing of infection events and allowed us to maximize the number of patients. As shown in Table 2, decreased mHLA-DR expression < 11 000 AB/C at D7 post-LT (odds ratio = 12.1 [4.4–38.2]) was independently associated with the occurrence of post-LT infections.

A MELD score > 30 was also significantly associated with post-LT infections in the model (odds ratio = 4.9 [1.4–18.4])), whereas the number of red blood cell units transfused and baseline mHLA-DR expression were not.

Infection-free survival curves, categorized by patients with D7 mHLA-DR levels below or above

Table 1 Recipient's, donor's and transplantation characteristics according to the occurrence of post-LT infections

Recipient's characteristics	Post-LT infections n = 35	No post-LT infections n = 64	*p*
Age (years)	53 [45–60]	58 [50–61]	0.11
Sex (male)	31 (88.6)	49 (76.6)	0.24
Severity			**0.02**
cACLD	**5 (14.3)**	**15 (23.4)**	
N-AD	**6 (17.1)**	**17 (26.6)**	
AD	**4 (11.4)**	**16 (25.0)**	
ACLF	**16 (45.7)**	**15 (23.4)**	
ALF	**4 (11.4)**	**1 (1.6)**	
ACLF Grade			**0.02**
No ACLF	**15 (42.8)**	**48 (75.0)**	
ACLF 1–2	**9 (25.7)**	**10 (15.6)**	
ACLF 3	**7 (20.0)**	**5 (7.8)**	
HCC	10 (28.6)	24 (37.5)	0.50
OF at LT (ACLF + ALF)	**20 (57.1)**	**16 (25.0)**	**0.003**
Hospitalized when called for LT	**19 (54.2)**	**15 (23.4)**	**0.004**
MELD score at LT	24 [18–39]	19 [15–26]	0.05
SOFA score at LT	5 [2–12]	4 [2–6]	0.11
Donor's characteristics			
Age (years)	69 [51–74]	65 [51–70]	0.54
Sex (male)	18 (51.4)	45 (70.3)	0.10
BMI (kg/m2)	25 [23–27]	25 [22–28]	0.89
DCD	2 (5.7)	15 (23.4)	0.05
Liver transplantation			
Cold ischemia (min)	398 [330–466]	393 [324–470]	0.71
Warm ischemia (min)	37 [29–40]	37 [25–41]	0.73
Surgery time (min)	385 [307–502]	377 [322–430]	0.46
RBC's transfused	**4 [2–8]**	**2 [0–5]**	**0.005**
Lactate's peak	4.9 [3.3–8.5]	4.0 [3.2–5.7]	0.16
Corticosteroids > 7 days	3 (8.6)	9 (14.1)	0.63

Results are expressed as medians and interquartile ranges [IQR] or numbers and percentages (%)

Bold values indicate significance of *p* value ($p < 0.05$)

ACLF acute on chronic liver failure, AD acute decompensation, ALD alcohol-related liver disease, ALF acute liver failure, BMI body mass index, cACLD compensated advanced chronic liver disease, CD cluster of differentiation, dACLD decompensated advanced chronic liver disease, DCD donation after circulatory death, HCC hepatocellular carcinoma, N-AD non acute decompensation, MELD Model for End-Stage Liver Disease, OF organ failure, RBC red blood cell, SOFA sequential organ failure assessment. Chi-square or Fisher's exact test was used for qualitative variables assessment. Quantitative variables were compared with Mann–Whitney U test or Kruskal–Wallis test

11,000 AB/C, are depicted in Fig. 3B. These curves significantly demonstrated that lower post-LT mHLA-DR values were associated with a greater occurrence of infections.

Lack of association of immune parameters with the occurrence of graft rejection

Acute graft rejection was documented on liver biopsy in 14 patients, within a median of 9 [6–11] days after LT, with a median BANFF score of 5 [5, 6]. As shown in Supplementary Table 2, no clinical factors were associated with the occurrence of acute graft rejection, nor were any immune markers (Supplementary Fig. 2).

Association with 1-year mortality

Among LT patients, the 1-year survival rate was 91.9%. The patient, donor and transplantation characteristics according to 1-year mortality are described in Table 3.

Nonsurvivors experienced more complications after their LT, including infections (75% vs. 32%, $p = 0.04$), surgical revisions (75% versus 31%, $p = 0.03$), and graft dysfunction (defined according to Olthoff's criteria [20], 75% vs. 27%, $p = 0.02$). However, nonsurvivors did not experience acute graft rejection (0% vs. 15%,

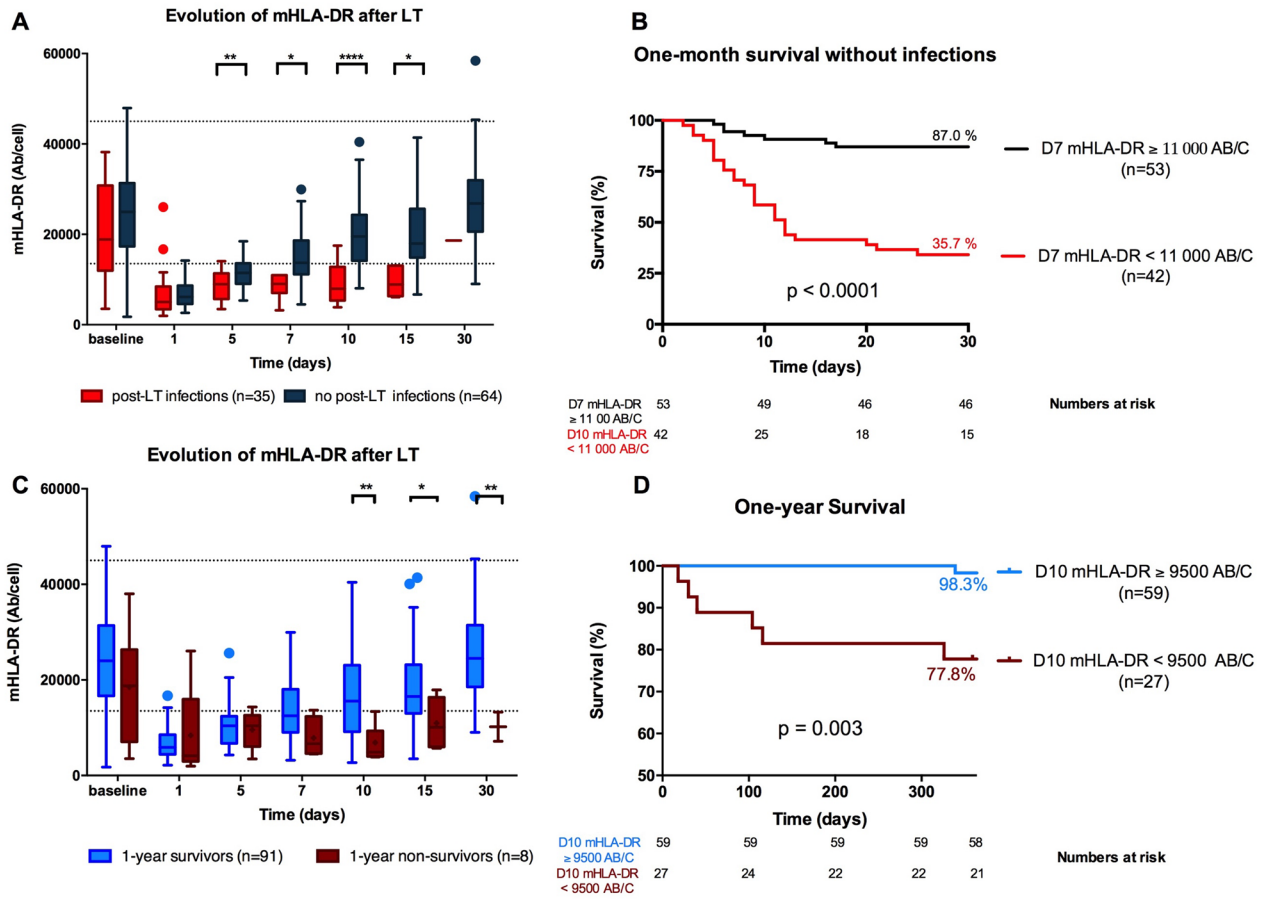

Fig. 3 Monocytic expression of HLA-DR (mHLA-DR) after liver transplantation (LT) and post-LT outcomes. Evolution of mHLA-DR according to the occurrence of infection (**A**) and survival without infection according to D5-7 mHLA-DR[a] (**B**). Evolution of monocytic expression of HLA-DR after liver transplantation (LT) according to one-year survival (**C**). One-year survival according to D10 mHLA-DR[b] (**D**). AB/C: antibodies per cell, LT: liver transplantation, mHLA-DR: monocytic HLA-DR; dotted lines represent the lower (i.e., 13,500 AB/C) and upper (i.e., 45,000 AB/C) limits of normal values. The Mann—Whitney U test was used for comparisons. Survival curves were generated via Kaplan—Meier estimates, and differences were compared via the log-rank test. *$p < 0.05$, **$p < 0.10$, ***$p < 0.001$, ****$p < 0.001$. [a] Survival curves generated in 95 out of 99 patients in whom D5-7 mHLA-DR was available. [b] Survival curves generated in 86 out of 99 patients in whom D10 mHLA-DR was available

Table 2 Independent predictors of post-LT infections

	OR	*p*
MELD at LT > 30	**4.9 [1.4–18.4]**	**0.01**
D 7 mHLA-DR expression < 11 000 AB/C	**12.1 [4.4–38.2]**	**< 0.0001**

AB/C antibodies per cell, D day, LT liver transplantation, MELD Model for End-Stage Liver Disease, mHLA-DR monocytic HLA-DR, 96/99 patients included in the multivariate analysis

Bold values indicate significance of *p* value ($p < 0.05$)

$p = 0.50$). Immune alterations were more severe in patients who died within the first year after LT. Regarding mHLA-DR, differences were observed starting from D10 (median 4900 AB/C [4300–8800] vs 15,600 AB/C [9200–23000], respectively, in nonsurvivors and survivors, $p = 0.002$) through D30 (median 10,200 [8700–11700] versus 24,500 [18600–31300], respectively, in nonsurvivors and survivors, $p = 0.03$). No difference was found according to baseline mHLA-DR expression (Fig. 3C, Supp Table 3). Total lymphocyte, T cell, CD4 and CD8 T-cell counts were also lower in nonsurvivors than in survivors but only at D10 (Supp Table 3, Supp Fig. 3), whereas no difference in IFN-γ levels released following stimulation was found. At D10, the mHLA-DR AUC for the prediction of one-year post-LT mortality was 0.86 (95% CI [0.75–0.97], $p = 0.001$), with an optimal cut-off value of 9500 AB/C (Se: 86%, Sp: 73%). At D15, the mHLA-DR AUC was 0.75 (95% CI [0.55–0.95], $p = 0.04$), with an optimal cut-off value of 15,800 AB/C (Se: 83%, Sp: 53%). At D30, the mHLA-DR AUC was 0.96 (95% CI [0.91–1.00], $p = 0.02$), with an optimal cut-off value of 13 500 AB/C

Table 3 Recipient's, donor's and transplantation characteristics according to one-year survival

Recipient's characteristics	Non-survivors n = 8	Survivors n = 91	*p*
Age (years)	**45 [41–55]**	**56 [49–62]**	**0.02**
Sex (male)	5 (62.5)	75 (82.4)	*0.37*
Severity			**0.02**
cACLD	**0 (0)**	**20 (24.7)**	
N-AD	**0 (0)**	**23 (28.4)**	
AD	**2 (25.0)**	**18 (22.2)**	
ACLF	**4 (50.0)**	**27 (33.3)**	
ALF	**2 (25.0))**	**3 (3.7)**	
ACLF Grade			**0.02**
No ACLF	**2 (25.0)**	**61 (67.0)**	
ACLF 1–2	**1 (12.5)**	**18 (19.8)**	
ACLF 3	**3 (37.5)**	**9 (9.9)**	
HCC	1 (12.5)	31 (38.3)	0.39
OF at LT (ACLF + ALF)	**6 (75.0)**	**30 (33.0)**	**0.04**
Hospitalized when called for LT	5 (62.5)	29 (31.9)	0.17
MELD score at LT	**35 [25–40]**	**19 [15–28]**	**0.03**
SOFA score at LT	**15 [4–17]**	**4 [2–16]**	**0.02**
Donor's characteristics			
Age (years)	63 [47–70]	66 [51–73]	0.50
Sex (male)	3 (37.5)	60 (65.9)	0.22
BMI (kg/m2)	27 [25–30]	25 [22–28]	0.12
DCD	0 (0)	17 (18.7)	*0.39*
Liver transplantation			
Cold ischemia (min)	380 [350–467]	395 [325–448]	0.89
Warm ischemia (min)	41 [34–54]	37 [27–41]	0.12
Surgery time (min)	363 [333–538]	380 [308–448]	0.59
RBC's transfused	**8 [6–9]**	**2 [0–5]**	**0.0004**
Lactate's peak	**11.1 [6.3–14.0]**	**4.0 [3.2–6.2]**	**0.0007**
Corticosteroids > 7 days	3 (8.6)	9 (14.1)	0.63

Results are expressed as medians and interquartile ranges [IQR] or numbers and percentages (%)

Bold values indicate significance of *p* value ($p < 0.05$)

ACLF acute on chronic liver failure, AD acute decompensation, ALD alcohol-related liver disease, ALF acute liver failure, BMI body mass index, cACLD compensated advanced chronic liver disease, CD cluster of differenciation, dACLD decompensated advanced chronic liver disease, DCD donation after circulatory death, HCC hepatocellular carcinoma, N-AD non acute decompensation, MELD Model for End-Stage Liver Disease, OF organ failure, RBC red blood cell, SOFA sequential organ failure assessment. Chi-square or Fisher's exact test was used for qualitative variables assessment. Quantitative variables were compared with Mann–Whitney U test or Kruskal–Wallis test

(Se: 100%, Sp: 94%). The survival curves categorized by D10 mHLA-DR levels (< 9500 AB/C) revealed a poorer prognosis in patients with low mHLA-DR values, based on an analysis of the 86 patients (out of the 99) for whom D10 mHLA-DR values were available). The small number of deceased patients (n = 8) prevented us from achieving sufficient statistical power to conduct a multivariate analysis.

K-means clustering analysis

Given the heterogeneity of post-LT mHLA-DR expression kinetics, we performed an in-depth K-means clustering analysis to identify distinct mHLA-DR expression patterns over time. This method allowed us to classify patients on the basis of their recovery trajectories, providing a clearer understanding of how immune status evolves after transplant and its impact on clinical outcomes (Fig. 4).

While all clusters started with mHLA-DR values below 10,000 AB/C, they primarily differed from each other in their recovery slope and thus the day on which their median values returned to normal levels (i.e., 13,500 AB/C). Cluster 1 (n = 35) started with a median value of 4100 AB/C [2900–5000] at D1 and reached the normal range by D20. Cluster 2 (n = 46) started with a median value of 6400 AB/C [5300–8900] and reached

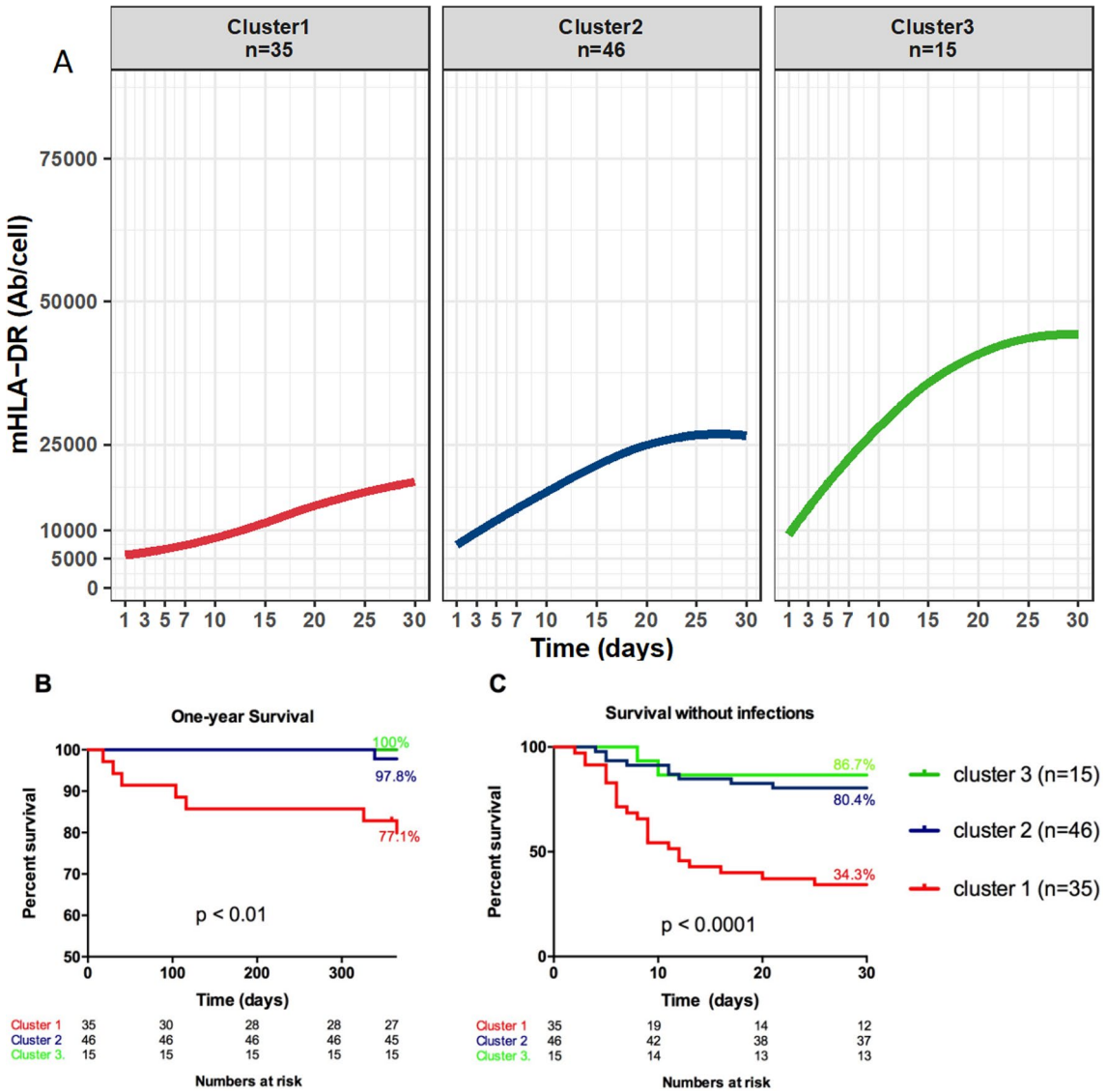

Fig. 4 Monocytic expression of HLA-DR trajectories post-liver transplantation and their impact on survival outcomes. **A** Trajectory of mHLA-DR expression after LT according to unsupervised clustering with the KmL method in the LT group (n = 96). The shaded interval corresponds to the normal values previously reported for healthy volunteers. **B** One-year survival according to the mHLA-DR endotype. **C** One-month survival without infections according to the mHLA-DR endotype. Ab/cell: antibodies per cell, KmL: k-means for longitudinal data, LT: liver transplantation, mHLA-DR: monocytic HLA-DR

the normal range by D7. Cluster 3 (n = 15) started with a median value of 7800 AB/C [6200–9700] and reached the normal range by D3. Several recipient, donor, and transplantation characteristics were significantly associated with cluster distribution (Table 4).

Notably, while patients with pre-LT organ failure were predominant in Cluster 1, ALF and ACLF patients were also represented in Clusters 2 and 3 but in lower proportions.

Consistent with previous findings (i.e., parameters analysed in a static context), the clusters also demonstrated significant differences in clinical outcomes. Cluster 1 had more infections and lower survival rates, Cluster 2 had less severe deterioration than did Cluster 1, and Cluster 3 had the best outcomes (Table 4, Fig. 4B, C). Most importantly, multivariate analysis revealed that belonging to Cluster 1 (compared with the other two clusters) was an independent parameter significantly associated with the occurrence of infections (odds ratio of 7.5, $p < 0.001$), as was having a MELD score > 30 at the time of the transplant (Table 5).

Table 4 Recipients, donors, LT characteristics and outcome according to mHLA-DR endodypes trajectories

	Cluster 1 n = 35	Cluster 2 n = 46	Cluster 3 n = 15	
Recipient's characteristics				
Age	**52 [44–57]**	**59 [51–61]**	**62 [52–64]**	**0.03**
Sex	30 (85.7)	37 (80.4)	11 (73.3)	0.58
Severity				0.08
cACLD	5 (14.3)	9 (19.6)	6 (40.0)	
N-AD	5 (14.3)	14 (30.4)	4 (26.7)	
AD	6 (17.1)	11 (23.9)	3 (20.0)	
ACLF	15 (42.9)	11 (23.9)	2 (13.3)	
ALF	4 (11.4)	1 (2.2)	0 (0)	
ACLF Grade				0.06
No ACLF	16 (45.7)	34 (73.9)	13 (86.7)	
ACLF 1–2	7 (20.0)	7 (15.2)	2 (13.3)	
ACLF 3	8 (22.9)	4 (8.7)	0 (0.0)	
HCC	9 (25.7)	16 (34.8)	8 (53.3)	0.17
OF at LT (ACLF + ALF)	**19 (54.2)**	**12 (26.1)**	**2 (13.3)**	**0.005**
Hospitalized when called for LT	**19 (54.3)**	**12 (26.1)**	**1 (6.7)**	**0.002**
MELD score at LT	**24 [17–40]**	**19 [15–27]**	**15 [9–20]**	**0.02**
SOFA score at LT	**5 [4–12]**	**4 [2–6]**	**4 [1–5]**	**0.03**
Baseline mHLA-DR (AB/C)	**17,800 [6800–25800]**	**25,000 [18700–29900]**	**33,400 [25900–36900]**	**0.0005**
Donor's characteristics				
Age (years)	69 [58–73]	64 [48–71]	63 [58–72]	0.33
Sex (male)	17 (48.6)	33 (71.7)	10 (66.7)	0.09
BMI (kg/m2)	25 [23–29]	24 [22–28]	24 [23–27]	0.62
DCD	4 (11.4)	8 (17.4)	5 (33.3)	0.18
Liver transplantation				
Cold ischemia (min)	430 [337–514]	373 [320–448]	410 [355–463]	0.21
Warm ischemia (min)	**40 [32–45]**	**36 [26–40]**	**29 [24–38]**	**0.01**
Surgery time (min)	**440 [319–523]**	**375 [305–420]**	**348 [298–430]**	**0.03**
RBC's transfused	**4 [2–8]**	**2 [0–5]**	**0 [0–2]**	**0.0002**
Lactate's peak	**6.1 [3.4–8.6]**	**3.8 [3–5.4]**	**4.0 [3.4–4.7]**	**0.04**
Corticosteroids > 7 days	6 (17.1)	5 (10.9)	1 (6.7)	0.53
Outcome				
Infections	**23 (65.7)**	**9 (19.6)**	**2 (13.3)**	**< 0.001**
Graft rejection	5 (14.3)	7 (15.2)	2 (13.3)	0.99
Surgical complications	**25 (71.4)**	**20 (43.5)**	**3 (20.0)**	**0.002**
Graft dysfunction (EAD)	**18 (51.4)**	**10 (21.7)**	**1 (6.7)**	**0.002**
Length of stay (LOS)				
Intensive care LOS (days)	**13 [6–30]**	**7 [5–10]**	**5 [5–7]**	**0.001**
Hospital LOS (days)	**29 [15–50]**	**21 [16–29]**	**14 [13–28]**	**0.03**
Organ support				
Total duration of vasopressors (days)	**2 [1–7]**	**1 [1, 2]**	**2 [1, 2]**	**0.003**
Total duration of MV (days)	**2 [1–9]**	**1 [1–1]**	**1 [1, 2]**	**< 0.001**
RRT	**18 (51.4)**	**6 (13.0)**	**1 (6.7)**	**< 0.001**
One-year survival	**29 (82.9)**	**45 (97.8)**	**15 (100)**	**0.03**

Results are expressed as medians and interquartile ranges [IQR] or numbers and percentages (%). DCD donation after circulatory death. EAD early allograft dysfunction, LOS length of stay, MV mechanical ventilation, RRT renal replacement therapy. Chi-square or Fisher's exact test was used for qualitative variables assessment. Quantitative variables were compared with Mann–Whitney U test

Bold values indicate significance of *p* value ($p < 0.05$)

Table 5 Independent predictors of post-LT infections after clustering analysis

	OR	*p*
MELD at LT > 30	3.6 [1.1–12.1]	**0.03**
Cluster 1	7.5 [2.9–20.9]	**< 0.0001**

LT liver transplantation, OF organ failure, MELD Model for End-Stage Liver Disease, D day, mHLA-DR: monocytes expression human leukocyte antigen-DR. 96/99 patients included in the multivariate analysis

Bold values indicate significance of *p* value ($p < 0.05$)

Discussion

LT is a key treatment for the management of patients with end-stage liver disease. However, infections remain a major complication in the post-transplant period and are the leading cause of early mortality, despite substantial advancements in the field. For example, a large retrospective study revealed that infections are the most frequent cause of death within 3 months post-LT for ACLF patients and the second most common cause of death for patients without pre-LT ACLF [1]. Among the various risk factors for infections following LT, the nature and intensity of the immunosuppression protocol are obviously important considerations. Nevertheless, monitoring immune parameters is not yet routinely used for this purpose. In this context, the present study aimed to assess cellular immune functions via standardized tools available in routine care to investigate the associations between immune parameters and outcomes, particularly the occurrence of infections in patients undergoing LT. Overall, we observed that all immune parameters significantly decreased after LT, but the magnitude of these initial decreases was not associated with any specific outcome. More importantly, the kinetics of parameter restoration provided valuable insights. Among these parameters, mHLA-DR expression has emerged as the most informative. To the best of our knowledge, we showed for the first time that, after LT, delayed restoration of mHLA-DR expression was strongly and independently associated with poor outcomes, notably with the risk of developing early severe infections.

In the present study, delayed restoration of mHLA-DR expression from day 5 onwards was associated with the occurrence of subsequent infections. This association was particularly strong from D7, where multivariate analysis (including all clinical confounders) identified mHLA-DR expression as a highly significant independent predictor of infection (OR: 12.1, $p < 0.001$), alongside the MELD score before LT. In addition to static analyses (i.e., time point by time point), the K-means clustering analysis revealed that mHLA-DR trajectories offered comparable insights into the slope of mHLA-DR restoration and the associated risk of infection. This highlights the interest in longitudinal monitoring of LT patients. The present work extends very preliminary studies obtained in the setting of transplantation, in which associations between low mHLA-DR levels and infectious risk have been reported in kidney and lung transplantation [21, 22]. Two previous studies, with very low numbers of patients (9 and 20, respectively), also suggested similar associations with LT [23, 24]. Given the substantial number of patients in our study (n = 99) and the improvements in several aspects, such as standardized measurements of mHLA-DR, clustering analysis, censorship of values once infection occurred, consideration of immune status before the transplant, and multivariate analysis, the present analysis strongly confirmed the association between post-LT mHLA-DR and infectious complications.

LT differs from other organ transplantations because of the heterogeneity of pre-LT conditions, which arises from the diverse indications for transplantation. For example, in our cohort, 36 patients experienced pre-LT organ failure, a condition associated with severe CAID [6, 25]. It is hypothesized that pre-LT immune status may impact post-LT outcomes, which is why we considered it in our analysis. Although baseline mHLA-DR expression was not an independent predictor of infections, its level was significantly lower in patients with delayed post-LT immune recovery (Cluster 1). Pre-LT immune status and pre-LT severity may not be sufficient to predict post-LT outcome and immune recovery. Clustering analysis revealed that 40% of the ACLF patients, and notably one third of grade 3 ACLF patients, were allocated to Clusters 2 and 3 (i.e., standard and fast post-LT immune recovery, respectively), which were associated with fewer infections and greater survival. Taken together, these data support the hypothesis that post-LT mHLA-DR kinetics may provide additional information beyond initial severity for monitoring infection risk.

The present work provides additional results: both static and clustering analyses highlighted an association between delayed mHLA-DR recovery and one-year mortality. Owing to the low number of cases, this aspect should be further assessed in larger cohorts. Additionally, no immune marker, including mHLA-DR, was associated with acute graft rejection in this study. Unexpectedly, post-LT lymphocyte count and function, assessed with an IFN-γ release assay, did not yield significant results for predicting outcome. This lack of association might be attributed to the homogenous immunosuppressive regimen, including anti-IL-2-R monoclonal antibodies, which target lymphocytes and potentially mask any underlying immune alterations related to post-LT outcomes. On the one hand, the unique immunosuppressive regimen administered to all patients included in our

study allowed us to ensure patient homogeneity. On the other hand, this may represent a limitation of our study, implying that our results need to be further confirmed in cohorts with different immune suppressive strategies. The monocentric nature of our study and some of the scores used for the reported clinical outcomes (eg Olthoff's EAD for graft dysfunction) represent another limitation to be acknowledged. A continuous evaluation of graft dysfunction, particularly using scores such as LGRAFT [26] or EASE [27], could be relevant.

As mentioned above, further studies are needed to determine how mHLA-DR expression monitoring may be incorporated into post-LT management. Specifically, larger cohorts are needed to validate the interest in post-LT mHLA-DR monitoring, regardless of immune suppressive regimens. These cohorts could be used to develop dynamic scores for the prediction of early infectious risk following LT. Recent studies have demonstrated that LT is an acceptable therapeutic strategy for critically ill patients, especially for Grade 3 ACLF patients [28–30]. However, post-LT prognostic factors are still debated for these patients [31, 32], and the development of individualized strategies for immune suppression and post-LT management may be useful in this setting. Since infections are among the most frequent causes of early death following LT [1], the identification of patients with a higher risk of infections could lead to the modulation of immune suppression to improve post-LT outcomes. Exploring these options in future clinical trials could provide valuable insights into optimizing posttransplant care. Moreover, understanding the underlying mechanisms driving different mHLA-DR trajectories and their impact on immune recovery can pave the way for novel targeted therapeutic interventions.

Conclusion

This study provides the first longitudinal monitoring of mHLA-DR expression before and after LT and its association with clinical outcomes. Delayed mHLA-DR restoration, whether measured at specific time points or assessed through trajectory clustering, was a significant independent predictor of future infection, as were high pre-LT MELD scores. These findings underscore the importance of early immune monitoring and suggest the benefit of individualized transplant management to improve outcomes. Additional studies are warranted to validate these findings in multicenter settings with diverse immunosuppression protocols.

Abbreviations

AB/C	Antibodies bound per cell
ACLD	Advanced chronic liver disease
ACLF	Acute-on-chronic liver failure
AD	Acute decompensation
ALD	Alcohol-related liver disease
ALF	Acute liver failure
cACLD	Compensated advanced chronic liver disease
CAID	Cirrhosis-associated immune dysfunction
dACLD	Decompensated advanced chronic liver disease
DCD	Donation after circulatory death
EAD	Early allograft dysfunction
EASE	Early allograft failure simplified estimation
HCC	Hepatocellular carcinoma
ICU	Intensive care unit
IFN-γ	Interferon-gamma
IL	Interleukin
KmL	K-means for longitudinal data
LGRAFT	Liver graft assessment following liver transplantation
LT	Liver transplantation
MASH	Metabolic dysfunction associated steatohepatitis
MELD	Model for end-stage liver disease
NAD	Nonacute decompensation
mHLA-DR	Monocytic Human Leukocyte Antigen-DR isotype
OF	Organ failure
SOFA	Sequential organ failure assessment
STROBE	Strengthening the reporting of obsvervational studies in epidemiology
WL	Waiting list

Supplementary Information

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Additional file 1.

Additional file 2.

Additional file 3.

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Author contributions

MCD: Conceptualization, Methodology, Resources, Data curation, Formal analysis, Investigation, Writing—original draft, Writing—review and editing. AR: Resources, Data curation, Formal analysis, Investigation, Writing—review and editing. TA: Resources, Writing—review and editing. TS: Data curation. MB: Methodology, Resources, Formal analysis, Investigation, Writing—review and editing. EP: Resources, Investigation, Writing—review and editing. FV: Resources, Writing—review and editing. MG: Resources, Writing—review and editing. SP: Conceptualization, Methodology, Writing—review and editing. JYM: Resources, Writing—review and editing. XM: Resources, Writing—review and editing. KM: Resources, Writing—review and editing. FV: Resources, Writing—review and editing. ED: Resources, Writing—review and editing. JD: Resources, Writing—review and editing. FZ: Resources, Writing—review and editing. LH: Conceptualization. CG: Resources, Writing—review and editing. AB: Resources, Writing—review and editing. FA: Resources, Writing—review and editing. GM: Conceptualization, Methodology, Resources, Investigation, Writing—original draft, Writing—review and editing. FL: Conceptualization, Methodology, Resources, Investigation, Writing—original draft, Writing—review and editing. All authors approved the final version.

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Availability of data and materials
The datasets generated and analysed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the *Comité de Protection des Personnes Ile de France* XI (approval number 19039-40433). Written informed consent was obtained from all participants prior to enrollment. The study complied with the Declaration of Helsinki. The study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Consent for publication
Not applicable.

Competing interests
MB and EP are employees of BioMérieux SA, an in vitro diagnostic company. MCD, MB, EP, FV, MG and GM work in a joint research unit, co-funded by the Hospices Civils de Lyon and bioMérieux.

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