Acute cellular rejection in adult liver transplant recipients in Johannesburg, South Africa

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Background. Wits Donald Gordon Medical Centre (WDGMC) in Johannesburg, South Africa, established a liver transplant programme in 2004. Acute cellular rejection (ACR) of the transplanted liver is a serious complication because of the potential for graft loss. ACR is defined as allograft dysfunction secondary to predominantly T-cell-mediated injury to the graft, and has been reported in up to 50% of liver transplants worldwide. While the advent of tacrolimus-based immunosuppression reduces the incidence of ACR in liver transplant recipients, it remains a concern.
Objectives. To review the incidence and risk factors for ACR, as well as the impact of ACR on graft survival in adult liver transplant recipients at WDGMC.
Methods. This was a retrospective review of first-time adult liver transplants performed from 1 January 2014 to 31 December 2022. Data collected included donor and recipient sociodemographic and clinical characteristics; transplant surgical procedure details; postoperative surgical complications; overall post-transplant ACR incidence rates in the first 365 days; ACR incidence stratified as early (≤90 days) and late (>91 days - <365 days); diagnosis and treatment details of biopsy-proven ACR episodes, including steroid resistance; and graft survival.
Results. Of 326 first-time adult liver transplants performed during the review period, 295 were eligible for inclusion. The post-transplant ACR incidence rates were 10.7% (early), 8.8% (late) and 20.3% overall (first 365 days). Corticosteroid resistance occurred in 19% of adult liver transplant recipients with biopsy-proven ACR. Risk factors for early ACR were younger recipient age, black ethnicity and male-donor-to-female-recipient sex discordance. A higher pre-transplant model for end-stage liver disease (MELD) score was a risk factor in late ACR. Younger recipient age, black ethnicity, female sex, acute liver failure, lower donor risk index scores and postoperative biliary complications were associated with increased risk for ACR in the first 365 days. ACR was not significantly associated with increased graft loss in this cohort.
Conclusion. While the incidence of ACR was low in this cohort, identification of ACR risk factors and presence of steroid-resistant ACR indicate the need for personalised and context-specific immunosuppression.

Keywords: acute cellular rejection, adult liver transplant

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Liver transplantation has been established as the standard of care for medically unresponsive acute liver failure and decompensated end-stage liver disease.[1-6] In Johannesburg, South Africa (SA), the Wits Donald Gordon Medical Centre (WDGMC), a private academic teaching hospital in the Faculty of Health Sciences at the University of the Witwatersrand, has been performing adult liver transplants and managing their complications since 2004.[1,2,5] Acute cellular rejection (ACR) of the transplanted graft is among the more serious complications encountered in liver transplantation because of the potential for ACR to cause graft loss.[1,2,5,7-9] Published literature reports that ACR occurs in up to 50% of adult liver transplant recipients.[7,10,11]

Acute rejection is defined as allograft dysfunction secondary to specific immune-mediated histopathological injury to the graft.[3,4,9] Various forms of acute rejection exist, and include ACR (a predominately T-cell-mediated graft injury), acute antibody-mediated rejection (an antibody-mediated graft injury) and acute mixed rejection (a combination of both forms of rejection).[3,4,12] Although the term 'acute' implies the temporal nature of when acute rejection occurs – typically within weeks to months post transplant – it is the histological changes (portal inflammation, bile duct injury secondary to inflammation, venous endothelial inflammation) noted in the graft that lend credence to the diagnosis of acute rejection.[9,12,13] Among the various forms of acute rejection, ACR in the liver graft comprises 99% of acute rejection episodes.[13-16] Additionally, T-cell-mediated rejection (TCMR) contributes to 99% of ACR episodes.[14-16] For this reason, ACR and TCMR have been used interchangeably to refer to the same clinico-histopathological entity.[11-13,17,18] While the 2016 Banff guideline[12] referred to ACR as the older term for TCMR,

in this study, the term ACR has continued to be used, as in other studies.[7,8,11,14,16]

The early post liver transplant period is associated with heightened immunological vigilance, as the immune system is exposed to the new allograft.[7-9] As such, the highest incidence of ACR has generally been in the first 3 - 6 months post transplant.[7-10,13] As a result, ACR is often divided between early and late ACR. A comprehensive review of ACR literature in terms of classification, detection, pathophysiology, risk factors, prevention and treatment has yet to achieve consensus on when early ACR v. late ACR occurs.[7-9,12,13,18,19-26] Some authors have suggested 1, 3 and 6 months as the cut-off separating early v. late ACR,[7-,9,12,19] partly due to the considerable overlap in histological features.[12] Unlike late ACR, which has been associated with progression to chronic allograft rejection and graft loss, data on early ACR graft outcomes are conflicting.[3,4,7-9,19,27] In this liver transplant programme, early ACR is considered as ACR occurring before 90 days.[7]

Advances in immunosuppression have reduced the incidence of overall ACR to ~20 - 40% in most transplant centres.[3,4,7-9,13,22,23] When examining the incidence of early v. late ACR in the literature, early ACR incidence rates range from 12 to 40%, while late ACR incidence rates range between 7 and 40%.[8,9,11,19] In most centres globally, the histological diagnosis of an ACR episode is accompanied by a grading of the rejection episode's severity.[7,12,19] The commonly used grading is the 2016 Banff guideline rejection activity index (RAI).[12] Severity grading is necessary to determine the need for treatment with high-dose corticosteroids.[7-9,13,19,28] Most ACR episodes that require corticosteroid therapy are responsive to treatment, referred to as 'steroid-sensitive'.[7,29-31] The remaining episodes that do not respond are categorised as 'steroid-resistant' rejection episodes.[7,29-31] The incidence of steroid-resistant ACR has been estimated to be 10 - 15% in international studies, and has a worse prognosis than steroid-sensitive ACR.[29-31] Control of steroid-resistant ACR requires use of other treatment modalities such as anti-thymocyte globulin (ATG).[7,29-31]

Risk factors for developing ACR in liver transplants are well described.[7,26,27] These include: recipient factors (young age, female sex, black ethnicity, non-sarcopenic state), aetiological factors (autoimmune disease, acute liver failure), transplant factors (cytomegalovirus (CMV) sero-discordance, donor-recipient sex discordance, ABO-incompatible transplant), donor factors (increased donor risk index, increased cold ischaemic time), post-transplant complications (infections/sepsis, biliary complications) and post-transplant medical treatment factors (tacrolimus tortuosity).[7,16,26,27]

The adult liver transplant programme at WDGMC has previously presented its successes and challenges through various publications, but none has been dedicated to ACR and its impact on the outcomes of adult liver transplant recipients.[1,2,5-7,26,27] In this study, we examine the incidence of ACR, the risk factors for ACR and its impact on graft survival in adult liver transplant recipients at WDGMC.

Methods

Sample selection

This was a retrospective review of all first-time adult liver transplants performed at WDGMC from 1 January 2014 to 31 December 2022. Data for this analysis were accessed from the REDCap WDGMC Adult Liver Transplant Research Database[32,33] (University of the Witwatersrand Human Research Medical Ethics ref. no. M190723). Data were collected on number of early (≤90 days), late (between 91 and 365 days) and overall (first 365 days) biopsy-proven ACR episodes, details of severity and treatment for each biopsy-proven ACR episode. Data were also collected on recipient demographics (age, sex, ethnicity), recipient cause of liver failure, recipient model for end-stage liver disease (MELD) score, recipient body mass index, donor type (deceased or living), donor-recipient ABO blood group compatibility, donor-recipient sex match, liver donor risk index (DRI), donor-recipient CMV sero-status matching, graft type (whole, split/reduced, or living), use of extended criteria organ, graft recipient weight ratio, presence of simultaneous kidney transplant, postoperative surgical complications (vascular, biliary and enteric), surgical re-exploration prior to discharge, hospital length of stay (LOS) and graft survival outcomes in the first 90 days, between 91 and 365 days and overall 365-day. Retransplant recipients and those aged <18 years at time of transplant were excluded.

Definitions

Temporal definitions for ACR incidence were: (*i*) early ACR incidence – the percentage of residual functional grafts at the end of the first 90 days that had developed at least one episode of ACR within the 90 days; (*ii*) late ACR incidence – the percentage of residual functional grafts at the end of 365 days that had developed at least one episode of ACR between day 91 and day 365; (*iii*) overall ACR incidence – the percentage of residual functional grafts at the end of 365 days that had developed at least one episode of ACR during the entire 365-day period. Severity of ACR was based on the 2016 Banff guideline.[12] Episodes with a RAI score >4 were included for analysis. In the WDGMC adult liver transplant programme, prevention of rejection is achieved using steroid-based immunosuppressive induction therapy accompanied by predominantly tacrolimus-mycofenotilmofetil-based maintenance therapy. Although there are nuances to these therapies, such as the addition of basiliximab in the induction of AIH recipients,[27] induction and maintenance regimens are similar between recipients. Treatment of a significant ACR episode, when it does occur, follows the treatment guideline as highlighted in the appendix (https://coding.samedical.org/file/2372), and includes a 3-day pulse of 1 g of intravenous methylprednisolone. This may be repeated if indicated. Failure to respond to two steroid pulses comprises a steroid-resistant ACR episode, which requires alternative immunosuppressive therapy. The DRI was calculated according to the standardised formula provided by Feng.[20] LOS was defined as the number of days from transplant to discharge from WDGMC, and in-hospital deaths were excluded. Postoperative surgical complications were defined as transplant-related surgical complications that required either radiological intervention or surgical re-exploration. These complications included anastomotic and non-anastomotic bile duct strictures, anastomotic and cut surface bile leaks, hepatic artery thrombosis, portal vein thrombosis, portal vein stenosis, venous outlet thrombosis, venous outlet stenosis, inferior vena cava thrombosis, inferior vena cava stenosis, enteric perforations and enteric obstructions.

Sample size

Sample size estimation was based on the comparison of graft survival between the ACR and non-ACR groups. Given that the ACR group comprised ~10% of the total sample, and with accrual and final follow-up periods of 9 years and 1 year, respectively, at 80% power and 5% significance level, the sample size was adequate to detect significant hazard ratios (HRs) >2.0.

Data analysis

Univariate analysis was performed to compare categorical study variables between ACR groups using the χ^2 test (Fisher's exact test was used for 2 × 2 tables or where the requirements for the χ^2 test were not met). Continuous variables were compared by the independent samples *t*-test, or by the Wilcoxon rank sum test if the assumptions of the *t*-test were not met. Multivariable analysis was performed

using Cox proportional hazards regression to examine the effect of ACR on graft survival. The date of the last ACR episode (if any) was used as a time-varying covariate. All comparisons were made unadjusted, and adjusted for variables that differed significantly between the ACR groups: recipient age, cause of liver failure (acute/chronic), donor-recipient sex match, DRI score (replaced with a score of 1.0 for living donors) and biliary complications. Adjustment was achieved by including the additional variables in the regression model as covariates. Data analysis was carried out using SAS version 9.4 for Windows (SAS Institute Inc., USA). $P<0.05$ was considered statistically significant.

Results

A total of 344 adult liver transplants were performed within the study period, of which 326 were first transplants. Follow-up data for ACR was available for only 295 of these transplants. As shown in Table 1, 244 liver grafts survived the first 90 days, while 227 survived to 365 days. There were 68 ACR episodes, with 33 episodes in 29 recipients occurring in the early period and 35 episodes in 22 recipients occurring in the late period. Some recipients developed >1 episode of ACR. The incidence of early ACR was 10.7% (26/244), and late ACR was 8.8% (20/227). The overall ACR incidence in the cohort at 365 days was 20.3% (46/227). Additionally, 85% of ACR episodes were treated with a steroid pulse. Of the episodes treated with a steroid pulse, 19% were steroid resistant. When comparing early and late ACR episodes, the early ACR episodes had fewer episodes with Banff scores >4 (79% v. 91%) and higher steroid responsiveness (87% v. 67%), and needed less alternative treatment.

Table 2 shows the various recipient, donor and transplant characteristics of the study group. Based on the tabulated characteristics, risk factors for early ACR included: younger median recipient age, non-white ethnicity and male-donor-to-female-recipient sex discordance (v. identical sex). High mean MELD score was a risk factor for late ACR. Risk factors for overall 365-day ACR episodes included younger median recipient age, black (v. white) ethnicity, female sex, acute (v. chronic) aetiology, liver DRI ≤1.8 and biliary complications.

Table 3 shows the outcomes following liver transplantation. Biliary complications were the only outcome associated with increased incidence of ACR in the first 365 days. With a median follow-up of 3.7 years and after adjusting for factors shown to differ significantly between early, late and overall ACR groups, the effect of ACR on graft failure was not significant (HR=1.76; 95% confidence interval 0.98 - 3.19; $p=0.061$).

Discussion

In the present study, the incidence of early ACR was 10.7%, lower than in most international studies.[8,9,11,20] Additionally, at 8.8% and 20.3%, the late and overall 1-year incidences of ACR were at the lower end of reported ACR incidences.[9,19] Although both early and late ACR episodes were not significantly associated with graft loss in this study, late ACR episodes may have represented more severe episodes, as evidenced by the higher proportion of episodes with Banff scores >4 (91% v. 78%), lower steroid responsiveness (67% v. 87%) and greater need for alternative treatment.

Like in many centres, corticosteroid-based therapy was the first-line treatment for ACR episodes in this study,[7-9,13,19,29] with a surprisingly high steroid-resistant incidence. The high steroid resistance may suggest a genetic basis. Additionally, while steroid use is routine, dosing regimens vary, and may be a cause for the higher resistance episodes noted.[7-9,19,29]

The scarcity of liver allografts in SA has necessitated more intensive follow-up and judicious use of immunosuppression – particularly tacrolimus-based immunosuppression – in liver

Table 1. ACR episode characteristics of the study group

Characteristic	Early ACR	Late ACR	ACR in first 365 days
Functional grafts, *n*	244	227	227
Grafts with ≥1 ACR episodes, *n*	26	20	46
Incidence of ACR, %	10.7	8.8	20.3
ACR episodes, *n*	33	35	68
Banff score, *n* (%)			
<4	5 (15)	2 (6)	7 (10)
>4	26 (79)	32 (91)	58 (85)
Unknown	2 (6)	1 (3)	3 (4)
Treatment of ACR episode, *n* (%)			
Immunosuppression optimisation only	2 (6)	1 (3)	3 (4)
Steroid pulse (methylprednisolone)	29 (88)	29 (83)	58 (85)
Anti thymoglobulin (atg)	2 (6)	2 (6)	4 (6)
Rituximab	0 (0)	1 (3)	1 (2)
Infliximab	1 (3)	0 (0)	1 (2)
Bortezomib	1 (3)	2 (6)	3 (4)
Plasma exchange	1 (3)	6 (17)	7 (10)
Intravenous immunoglobulin	0 (0)	1 (3)	1 (2)
Retransplant	0 (0)	3 (9)	3 (4)
Unknown	1 (3)	0 (0)	1 (2)
ACR steroid sensitivity (*n*=58), *n* (%)*			
Sensitive	27 (87)	18 (67)	45 (78)
Resistant	3 (10)	8 (30)	11 (19)
Unknown	1 (3)	1 (3)	2 (3)

ACR = acute cellular rejection.
*n=31 for early ACR, n=27 for late ACR and ACR in first 365 days.

Table 2. Recipient, donor and transplant characteristics of the study group

Characteristic	Overall (*n*=295), *n* (%)*	Early ACR (244/295 functioning grafts) ACR incidence, %*	*p*-value	Late ACR (227/295 functioning grafts) ACR incidence, %*	*p*-value	ACR in first 365 days (227/295 functioning grafts) ACR incidence, %*	*p*-value
Overall		10.7	-	8.8	-	20.3	-
Recipient age, years, median (IQR)	54 (42 - 61)	ACR 46 (28 - 55); no ACR 54 (43 - 61)	0.032	ACR 46 (36 - 57); no ACR 53 (42 - 61)	0.21	ACR 46 (32 - 56); no ACR 54 (43 - 61)	0.015
Recipient sex							
Male	178 (60.3)	8.1	0.14	6.7	0.23	15.7	0.045
Female	117 (39.7)	14.6		11.8		26.9	
Recipient ethnicity							
Black	57 (19.3)	17.8	0.0006	12.8	0.13	38.3	0.0026
White	194 (65.8)	7.3		9.4		15.4	
Neither	44 (14.9)	23.7		0.0		16.1	
Cause of liver failure							
Acute	20 (6.8)	18.2	0.33	27.3	0.061	45.5	0.049
Chronic	275 (93.2)	10.3		7.9		19.0	
ASH/NASH	90 (30.5)	7.5	0.43	7.1	0.29	15.7	0.063
Cholestatic excluding AIH	68 (23.1)	14.3		10.9		25.5	
AIH	33 (11.2)	14.3		10.7		25.0	
Malignancy	30 (10.2)	8.3		0.0		10.0	
Metabolic	13 (4.4)	0.0		8.3		8.3	
Hep B	10 (3.4)	0.0		0.0		0.0	
Hep C	9 (3.1)	28.6		28.6		57.1	
Other	22 (7.5)	11.8		0.0		11.8	
MELD, mean (SD)	18 (8)	ACR 16 (5); no ACR 18 (7)	0.16	ACR 22 (7); no ACR 17 (7)	0.0042	ACR 18 (7); no ACR 17 (7)	0.39
BMI (kg/m^2), mean (SD)	26 (5)	ACR 27 (5); no ACR 26 (5)	0.42	ACR 26 (5); no ACR 26 (5)	0.95	ACR 26 (5); no ACR 26 (5)	0.49
Donor characteristics							
Donor type							
Deceased	269 (91.2)	10.5	0.68	9.0	>0.99	20.3	>0.99
Living	26 (8.8)	12.5		6.7		20.0	
ABO compatibility							
Compatible	266 (90.2)	10.5	0.72	8.7	0.66	19.7	0.38
Incompatible	29 (9.8)	13.0		11.1		27.8	
Donor-recipient sex match							
Identical	169 (57.3)	7.2	0.023	10.2	0.81	18.0	0.21
Male to female	63 (21.4)	21.2		7.8		29.4	
Female to male	63 (21.4)	9.6		6.4		17.0	
Donor risk index (deceased donors)†							
<1.8	183 (71.5)	13.1	0.26	9.4	0.61	23.5	0.042
≥1.8	73 (28.5)	3.5		3.8		7.5	
CMV (IgG) serostatus matching‡							
Match	191 (68.0)	10.8	0.48	8.0	0.76	19.3	0.61
Donor +, recipient –	34 (12.1)	6.5		11.5		19.2	
Donor –, recipient +	56 (19.9)	15.2		9.5		26.2	
Transplant characteristics							
Graft type							
Whole	249 (84.4)	10.8	0.80	9.7	0.51	21.4	0.36
Split/reduced	21 (7.1)	5.9		0.0		5.9	
Living	25 (8.5)	13.3		7.1		21.4	

continued

transplant recipients in Johannesburg.[1,2,5,6,27] This approach has likely yielded the lower incidence of ACR noted in the cohort. Another, less likely reason may be the underdiagnosis of ACR. The potential for underdiagnosis, particularly subclinical rejection, does exist, as local protocols do not advocate protocolised biopsies, which may contribute to the lower ACR incidence reported.[19,34]

Similar to other studies, demographic and clinical factors in the present study associated with an increased risk of early ACR included younger recipient age, black ethnicity and donor-recipient sex discordance.[3,4,7-9,13,19,21,27] While studies have varied in demonstrating an association of higher MELD score with development of ACR, it was the only risk factor associated with late ACR in this cohort, and may represent challenges with balancing immunosuppression in sicker recipients.[8,35-38]

Within the first 365 days, female sex, acute aetiology, lower DRI and the presence of biliary complications were associated with an increased risk of ACR. The increased risk of ACR in younger and acute liver failure recipients may be related to an aggressive immune response observed in these individuals.[7,9,21,24,25] The association of female sex with increased ACR is postulated to be related to hormonal influences, particularly oestrogen, which enhances immune activity.[8,18,21] Sex-specific differences in drug metabolism may also contribute to suboptimal immunosuppression in women.[8,21] Regarding black ethnicity, this likely reflects the prevalence of specific HLA alleles that influence antigen presentation, immune activation and immunosuppressive drug metabolism.[7,26,27] These findings highlight the need for a tailored approach to immunosuppressive therapy.

Increased DRI has been shown to increase ACR due to increased ischaemia-reperfusion injury, which leads to an inflammatory cascade.[7] This cascade upregulates the innate and cell-mediated immune systems, reducing allograft tolerance.[7-9,13] Generation of T-memory cells additionally predisposes recipients to other ACR episodes.[7-9,13] Like increased DRI, biliary complications are thought to increase the incidence of ACR through a similar process, although through chemical or sepsis-related immune activation.[7-9,22] Unlike in other studies, increased DRIs were not significantly associated with increased ACR in this study. However, biliary complications were associated with an increased risk of ACR in the first 365 days.[7,8,19,27]

Conclusion

While the incidence of ACR in the present study was lower than that reported in other cohorts, the identification of high-risk demographic groups and the presence of steroid-resistant ACR highlight the need for personalised and context-specific approaches to immunosuppression. Continued research, particularly in resource-limited settings, is essential to optimise outcomes and to address the unique challenges of liver transplantation in Africa.

Table 3. Post-transplant outcomes in the study group

Post-transplant characteristic	Overall (*N*=295), *n* (%)*	Early ACR (244/295 functioning grafts) Incidence of ACR, %*	*p*-value	Late ACR (227/295 functioning grafts) Incidence of ACR, %*	*p*-value	ACR in first 365 days (227/295 functioning grafts) Incidence of ACR, %*	*p*-value
Overall		10.7		8.8		20.3	
Biliary complication(s), 90 days	74 (25.1)	15.8	0.22	9.8	0.78	27.5	0.17
Biliary complication(s), 365 days	93 (31.5)			13.0	0.20	31.9	0.0066
Vascular complication(s), 90 days	37 (12.5)	6.7	>0.99	16.7	0.29	25.0	0.71
Vascular complication(s), 365 days	44 (14.9)			11.1	0.66	27.8	0.37
Enteric complication(s), 90 days†	11 (3.7)	33.3	0.13	0.0	>0.99	33.3	0.60
Enteric complication(s), 365 days†	15 (5.1)			0.0	>0.99	22.2	>0.99
Surgical re-exploration, 90 days‡	74 (25.6)	7.8	0.61	11.1	0.56	20.0	>0.99
Surgical re-exploration, 365 days	81 (27.5)			10.2	0.78	18.4	0.84
Days in hospital after transplant, median (IQR)§	15 (12 - 24)	ACR 14 (14 - 26), no ACR 15 (11 - 23)	0.97	ACR 12 (11 - 16), no ACR 15 (12 - 24)	0.34	ACR 16 (12 - 21), no ACR 15 (11 - 23)	0.52
Graft survival (HR: ACR v. no ACR)¶	1.76 (95% CI 0.98 - 3.19) (*p*=0.061)						

ACR = acute cellular rejection; IQR = interquartile range; HR = hazard ratio; CI = confidence interval.
*Unless otherwise indicated.
†*n*=294 overall; *n*=243 for early ACR and *n*=226 for late ACR and ACR in first 365 days.
‡*n*=289 overall.
§Liver alone transplants; excluding deaths pre discharge; *n*=246 overall; *n*=237 for early ACR and *n*=221 for late ACR and ACR in first 365 days.
¶Median follow-up time was 3.7 years.

Data availability. Data available on written request to the author.

Declaration. None.

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