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Perioperative Desensitization in Immunologically High-Risk Living Donor Liver Transplantation: A Multicenter Comparative Study

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Abstract

Perioperative desensitization strategies for living donor liver transplantation (LDLT) recipients with immunologically high risk remain inconsistently defined across centers. This multicenter retrospective cohort study compared outcomes in 105 ABO-compatible LDLT recipients with donor-specific antibody (DSA) mean fluorescence intensity (MFI) ≥ 5,000 across two centers with different desensitization strategies (rituximab/plasmapheresis vs. none) between 2015 and 2023, with propensity score matching performed within immunologic risk strata. Desensitized recipients demonstrated lower crude rejection rates (25.5% vs. 36.0%) and significantly improved biliary complication–free survival (p = 0.023), with benefits most pronounced in high-risk recipients after propensity score matching, while overall survival and graft failure–free survival did not differ significantly between groups. These findings suggest that preoperative desensitization may attenuate early immune-mediated graft injury, particularly in high-risk LDLT recipients with elevated DSA burden, though survival benefits remain to be established.

Introduction

Liver transplantation (LT) has evolved beyond its original indication of end-stage liver disease, increasingly offered to patients with earlier stages including early hepatocellular carcinoma (HCC), or rather, advanced HCC with higher tumor burden [1, 2]. As indications continue to expand, the persistent shortage of deceased donors has driven widespread adoption of living donor liver transplantation (LDLT), which now constitutes a substantial proportion of transplant in South Korea [3, 4].

Given the liver's inherent immunologic tolerance compared to other solid organs, transplantation across traditional immunologic barriers, including ABO-incompatible (ABOi) donors and recipients with preformed donor-specific antibodies (DSAs), has become increasingly practiced [5–7]. While perioperative desensitization is routinely applied in ABOi LDLT, its role in DSA-positive recipients, particularly those with positive crossmatch results, has been less consistently defined [8].

The LDLT setting introduces additional complexity: smaller graft-to-recipient weight ratios and sensitization through prior pregnancy may heighten susceptibility to early immune-mediated graft injury [9, 10]. These competing considerations have resulted in substantial variability in desensitization practice across South Korean transplant centers. Many institutions rely on the liver's inherent immunologic privilege and forgo formal desensitization even in high-risk cases, whereas our center has implemented a protocol incorporating rituximab and plasmapheresis for recipients with preformed DSAs and/or positive crossmatch results (Fig. 1) [11].

In this multicenter retrospective study, we compared post-transplant outcomes between two high-volume Korean LDLT centers employing divergent perioperative desensitization strategies. We hypothesized that a systematic desensitization protocol would attenuate early immune-mediated graft injury including acute rejection and biliary complications, particularly in recipients with high immunologic risk profiles.

Results

Table 1
Baseline characteristics of patients stratified by desensitization status

Variable	No Desensitization (n = 50)	Desensitization (n = 55)	*p*
Age (mean (SD))	55.50 (8.55)	55.24 (7.71)	0.868
Sex (%) Male	13 (26.0)	10 (18.2)	0.465
MELD score (mean (SD))	13.99 (6.12)	13.04 (5.11)	0.390
GRWR (mean (SD))	1.24 (0.26)	1.24 (0.29)	0.978
Preop TB (mean (SD))	4.43 (7.80)	2.63 (2.06)	0.102
Preop INR (mean (SD))	1.41 (0.44)	1.32 (0.25)	0.184
Cold ischemic time (mean (SD))	128.66 (54.83)	110.15 (42.04)	0.054
Warm ischemic time (mean (SD))	55.08 (89.81)	35.76 (14.02)	0.118
Donor age (mean (SD))	32.36 (11.24)	34.47 (11.93)	0.354
Related (%)	41 (82.0)	45 (81.8)	1.000
Preop Hb (mean (SD))	10.12 (1.48)	9.95 (1.85)	0.624
DSA MFImax (mean (SD))	15705.42 (5777.58)	16848.04 (5479.90)	0.301
Ascites (%)	26 (52.0)	35 (63.6)	0.313
Risk group (%)			
High	25 (50.0)	27 (49.1)	1.000
Intermediate	15 (30.0)	23 (41.8)	0.229
Low	10 (20.0)	5 (9.1)	0.162

Data are presented as mean (SD) or n (%). GRWR, graft-to-recipient weight ratio; TB, total bilirubin; INR, international normalized ratio; Hb, hemoglobin; DSA, donor-specific antibody; MFImax, maximum mean fluorescence intensity; MELD, Model for End-Stage Liver Disease. Risk group classification was based on immunological risk stratification prior to transplantation. *P* values were calculated using Student's *t*-test for continuous variables and chi-square test or Fisher's exact test for categorical variables.

Patient Population and Baseline Characteristics

Among 141 patients who underwent LDLT with preformed DSAs (mean fluorescence intensity [MFI] ≥ 5,000), 36 ABO-incompatible recipients were excluded, with a final cohort of 105 patients (Fig. 2). Of these, 55 received perioperative desensitization and 50 did not. By immunologic risk stratum, 52 patients

(49.5%) were classified as high risk, 38 (36.2%) as intermediate risk, and 15 (14.3%) as low risk. Risk group distribution was broadly comparable between the two groups.

Baseline characteristics are summarized in Table 1. The desensitized and non-desensitized groups were well matched with respect to recipient age, sex, Model for End-Stage Liver Disease (MELD) score, graft-to-recipient weight ratio (GRWR), pretransplant laboratory values (total bilirubin, international normalized ratio [INR], and hemoglobin), donor age, donor–recipient relationship, and ischemic times. Peak DSA MFI values were similarly comparable between groups (16,848 ± 5,480 vs. 15,705 ± 5,778; p = 0.301), as was the distribution of immunologic risk categories (p > 0.05).

Rejection Rates

In the overall cohort, the crude rejection rate was lower in desensitized recipients than in non-desensitized recipients (25.5% vs. 36.0%; Fig. 3), with the most pronounced difference observed in the high-risk subgroup (Fig. 4). Although these differences did not reach statistical significance in the unmatched cohort, the directional consistency of findings across subgroups suggests that desensitization may attenuate acute rejection risk, particularly in recipients with high pretransplant DSA burden.

Rejection-Free and Biliary Complication–Free Survival

Kaplan–Meier analysis demonstrated a trend toward improved rejection-free survival (RFS) in desensitized recipients across the overall cohort (Fig. 5). This benefit was most pronounced in the high-risk subgroup, where the difference in RFS achieved statistical significance following propensity score matching, supporting the robustness of this association.

Biliary outcomes followed a similar pattern. Desensitized recipients demonstrated significantly improved biliary stricture–free survival compared with non-desensitized recipients in the overall cohort (p = 0.023; Fig. 6). This effect was most pronounced among high-risk recipients after propensity score matching, suggesting that immune-mediated biliary injury may be attenuated by perioperative desensitization.

Overall Survival and Graft Failure–Free Survival

Despite the early benefits observed in rejection and biliary outcomes, desensitization was not associated with a significant improvement in overall survival (OS) or graft failure–free survival (GFFS) in either the overall cohort or in the matched high-risk subgroup (Figs. 7 and 8).

Discussion

In this multicenter cohort of immunologically high-risk LDLT recipients, perioperative desensitization was associated with significantly improved rejection-free and biliary stricture–free survival, with the most

pronounced benefit observed in high-risk recipients. These associations remained after propensity score matching, supporting a role for desensitization in attenuating early immune-mediated complications in selected patients.

The pattern of early Kaplan–Meier curve separation and the lower initial hazard in the desensitization group suggest that the primary mechanism of benefit operates during the perioperative immunologic window. Rituximab-mediated B-cell depletion combined with plasmapheresis is thought to reduce circulating DSA titers, attenuate complement activation, and limit endothelial injury during the immediate post-transplant phase, which is believed to be vulnerable to antibody-mediated alloimmune injury [10, 12–14].

Our findings also support the principle that desensitization is not universally required for all preformed DSA-positive recipients, but should be reserved for those with the highest immunologic risk profile. The liver's inherent immunologic tolerance, attributed to its large parenchymal mass, unique sinusoidal microvasculature, constitutive expression of human leukocyte antigen (HLA) class I molecules without co-stimulatory signals, and active Kupffer cell–mediated clearance of circulating DSAs is known to provide a certain degree of tolerance compared to other solid organ transplants [5, 10, 15–17].

However, this tolerance is not absolute, especially in the LDLT setting. Living donors are frequently first-degree relatives, and prior sensitization through pregnancy or blood transfusion may amplify the alloimmune response upon re-exposure to shared HLA antigens from a spouse or offspring [18–20]. Moreover, partial liver grafts used in LDLT provides a reduced vascular bed relative to whole-organ grafts, potentially limiting the graft's capacity to absorb circulating antibodies [21].

Our protocol distinctively includes flow cytometry crossmatch (FCXM) and complement-dependent cytotoxicity (CDC) crossmatch results rather than relying on DSA MFI thresholds alone. This approach reflects the well-recognized limitations of single-antigen bead (SAB) assays in liver transplantation. Although SAB assays provide sensitive and specific DSA detection, antibody binding is measured in a cell-free environment that may not faithfully reflect the in vivo immunologic milieu of the transplanted graft. SAB assays are susceptible to false-positive results attributable to denatured HLA antigens on the bead surface, and elevated MFI values do not invariably correlate with complement-activating capacity or clinical pathogenicity [22–24]. Integrating functional crossmatch data with SAB-based DSA profiling therefore allows more accurate stratification of true immunologic risk and more precise identification of candidates likely to benefit from desensitization [13, 25]. Where available, complementary assays such as C1q binding or IgG subclass profiling may further refine risk assessment [25, 26].

Notably, desensitization seemed to have association to improved biliary stricture–free survival. Biliary complications after LDLT are traditionally known to be affected by technical or ischemic factors [27, 28]. However, our findings raise the possibility that antibody-mediated injury may also contribute to biliary pathology in highly sensitized recipients. Cholangiocytes constitutively express HLA class I molecules and may upregulate class II expression under inflammatory conditions, rendering them potential targets of circulating DSAs [29–31]. DSA-mediated endothelial and epithelial injury may amplify periductal

inflammation, microvascular dysfunction, and fibrosis, thereby lowering the threshold for biliary stricture formation in the setting of concomitant surgical and ischemic stress [31, 32]. This interpretation is consistent with our observation that desensitization did not eliminate biliary events entirely but appeared to prolong the biliary complication–free interval, particularly during the early postoperative period.

It should be noted, however, that the precise relationship between immunologic injury and biliary complications remains incompletely understood, and elucidating this mechanistic link was not an aim of the present study. The observed association is hypothesis-generating and should be interpreted with caution pending dedicated mechanistic and prospective investigations.

Although the predominant rejection phenotype in our cohort was T cell–mediated rejection (TCMR; approximately 50%), this should not be interpreted as evidence against a pathogenic role for preformed DSAs. Antibody-mediated rejection (AMR) in liver transplantation remains diagnostically challenging: C4d deposition is less reliable as a diagnostic marker than in other solid organ transplantation, histologic patterns frequently overlap, and mixed forms of alloimmune injury are likely underrecognized [10, 12]. Furthermore, experimental and clinical data suggest that preformed DSAs may facilitate T-cell activation indirectly through proinflammatory cytokine release and upregulation of endothelial adhesion molecules, thereby promoting T-cell infiltration even in the absence of classic AMR histology [33–35]. The predominance of TCMR in our cohort therefore does not exclude a meaningful biologic contribution from humoral sensitization. Additionally, both centers employed similar maintenance immunosuppression protocols, including similar calcineurin inhibitor trough targets and induction strategies, which minimizes the influence of background immunosuppression differences on the observed outcomes.

This study has several limitations. First, the overall sample size was modest, and subgroup analyses may have been underpowered to detect clinically meaningful differences. Second, protocol biopsies were not routinely performed at either center, and a subset of rejection episodes was diagnosed and treated empirically, introducing the possibility of misclassification. Third, detailed immunologic characterization including serial post-transplant DSA monitoring, IgG subclass profiling, and C1q binding data were not systematically available, precluding a more granular assessment of antibody dynamics and pathogenicity over time.

Despite these limitations, this study implies clinically significant conclusion that perioperative desensitization may improve early outcomes in a selected group of patients with high immunologic risk.

In conclusion, perioperative desensitization was associated with significantly improved rejection-free and biliary stricture-free survival in immunologically high-risk ABO-compatible LDLT recipients, with the greatest benefit observed in the high-risk subgroup. Although desensitization did not translate into improvements in overall survival or graft failure-free survival, it appeared to effectively attenuate early immune-mediated graft injury during the most vulnerable perioperative window. These findings support the adoption of a risk-stratified desensitization strategy in carefully selected, highly sensitized LDLT

recipients, and highlight the need for prospective multicenter studies to further define optimal candidate selection and protocol design.

Methods

Study Design and Patient Population

This retrospective, multicenter cohort study included adult patients who underwent ABO-compatible LDLT between 2015 and 2023 at two high-volume transplant centers in South Korea. Eligible recipients had preformed donor-specific anti-HLA antibodies (DSAs) with a mean fluorescence intensity (MFI) ≥ 5,000 on pretransplant solid-phase immunoassay. ABO-incompatible LDLT recipients were excluded.

Institutional Desensitization Strategies

At one center, a structured desensitization protocol was established in 2015 for recipients deemed at high immunologic risk. The protocol incorporates preoperative rituximab administration and perioperative plasmapheresis, with recipients stratified into low-, intermediate-, and high-risk groups according to pretransplant DSA MFI levels, flow cytometry crossmatch (FCXM) results, and complement-dependent cytotoxicity (CDC) testing (Fig. 1). Protocol adherence was not universal, as some recipients deviated from the assigned regimen due to clinical condition or operator discretion. Accordingly, this study was designed as a real-world institutional comparison of divergent immunologic management strategies rather than a strict protocol-adherence analysis. The comparator center did not employ a formal desensitization protocol during the same period, reflecting the prevailing practice among many South Korean transplant centers that rely on the liver's inherent immunologic tolerance.

DSA Assessment

Preformed DSAs were identified using a solid-phase immunoassay based on Luminex technology (LABScreen Single Antigen; One Lambda, USA). This platform utilizes polystyrene microspheres coated with purified individual HLA antigens, each encoded by a unique fluorescent signature, enabling single-antigen-level specificity and quantification.

Outcomes

The primary outcome was rejection-free survival (RFS), defined as the time from transplantation to the first clinically meaningful rejection episode. Rejection was defined as either histologically confirmed acute rejection or clinically suspected rejection empirically treated with high-dose steroid pulse therapy. As neither center performed routine protocol biopsies, a proportion of rejection episodes were diagnosed and treated on clinical grounds without histologic confirmation.

Secondary outcomes included: (1) overall survival (OS), defined as time from transplantation to death from any cause; (2) graft failure–free survival (GFFS), defined as time to graft failure or death; and (3)

biliary complication–free survival (BDCFS), defined as time to the first biliary stricture or leak requiring radiologic, endoscopic, or surgical intervention.

Statistical Analysis

Baseline characteristics were compared between desensitized and non-desensitized recipients using the chi-square test or Fisher's exact test for categorical variables, and the Student's t-test or Mann–Whitney U test for continuous variables, as appropriate. Survival outcomes were estimated by the Kaplan–Meier method and compared using the log-rank test.

Subgroup analyses were performed within each immunologic risk stratum (high, intermediate, and low). To minimize confounding, propensity score matching (PSM) was performed separately within each subgroup using a logistic regression model incorporating age, Model for End-Stage Liver Disease (MELD) score, pretransplant total bilirubin, international normalized ratio (INR), cold ischemic time, and graft-to-recipient weight ratio (GRWR). A 1:1 nearest-neighbor matching without replacement was performed using a caliper width of 0.2 standard deviations of the logit of the propensity score. Covariate balance after matching was assessed using standardized mean differences (SMDs).

All analyses were performed using R software (version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria). A two-sided p-value < 0.05 was considered statistically significant.

Declarations

Ethics declarations

This study was approved by the Institutional Review Board of Seoul National University Hospital (IRB No. 2504-017-1628). All methods were performed in accordance with the relevant guidelines and regulations and with the principles of the Declaration of Helsinki. The requirement for informed consent was waived by the Institutional Review Board of Seoul National University Hospital (IRB No. 2504-017-1628) owing to the retrospective design of the study.

Use of large language models

Claude (Anthropic), a large language model, was used for translation assistance, revision of sentence structure, manuscript formatting, and figure formatting and size adjustment. It was not used to generate study concepts, analyse data, interpret results, or draw conclusions. All AI-assisted content was reviewed and edited by the authors, who take full responsibility for the accuracy and integrity of the work. Data analysis and figure generation were conducted using R (R Foundation for Statistical Computing).

Additional information

Competing interests:

The authors declare no competing interests.

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Author Contribution

Min Kyoung Kim and Deok-Gie Kim contributed equally to this work and share first authorship. Dong Jin Joo and YoungRok Choi contributed equally to this work and share corresponding authorship. The specific contributions of each author are as follows: Dong Jin Joo and YoungRok Choi were responsible for the conception and design of the study. Min Kyoung Kim, Deok-Gie Kim, Su young Hong, Suk Kyun Hong, Kwang-Woong Lee, Dong Jin Joo and YoungRok Choi contributed to data acquisition. Min Kyoung Kim drafted the manuscript. All authors critically reviewed the manuscript for important intellectual content, approved the final version to be published, and agreed to be accountable for all aspects of the work.

Data Availability

The datasets generated and/or analysed during the current study are not publicly available owing to patient privacy restrictions but are available from the corresponding author on reasonable request.

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Figures

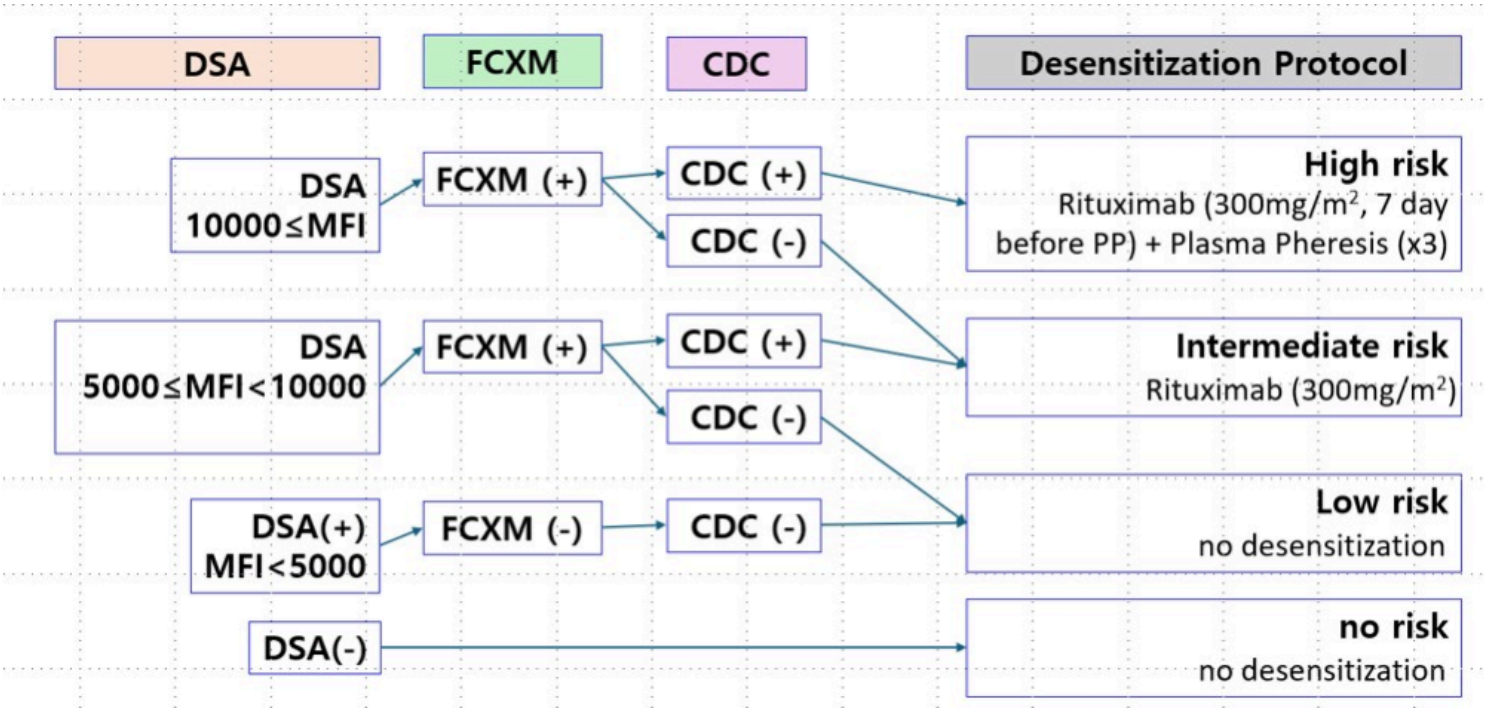


Figure 1

Institutional desensitization protocol stratified by immunological risk. Recipients were classified into risk groups based on donor-specific antibody (DSA) mean fluorescence intensity (MFI), flow cytometry crossmatch (FCXM) results, and complement-dependent cytotoxicity (CDC) results. High-risk recipients (DSA MFI ≥10,000 with FCXM positivity) received rituximab (300 mg/m², administered 7 days before plasmapheresis) combined with plasmapheresis (×3). Intermediate-risk recipients received rituximab alone (300 mg/m²). Low-risk recipients (DSA MFI <5,000 with FCXM and CDC negativity) and DSA-negative recipients were managed without desensitization.

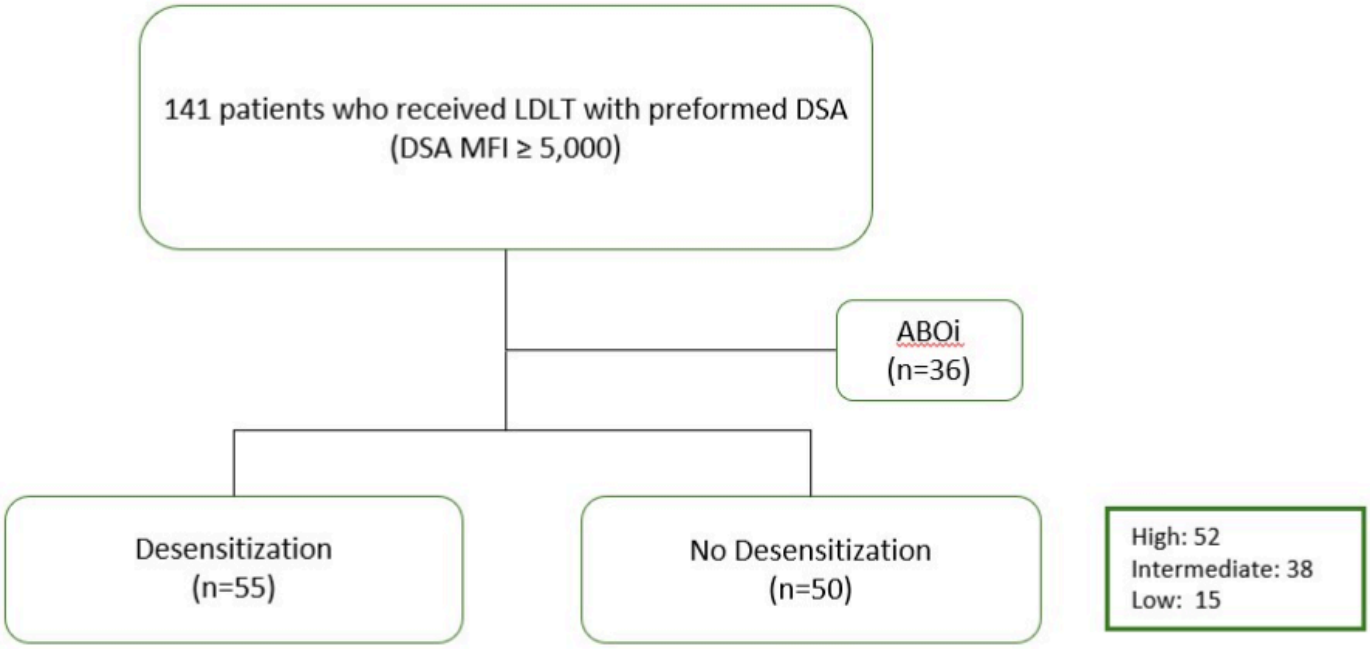


Figure 2

Study flow diagram. Of 141 patients who underwent living donor liver transplantation (LDLT) with preformed donor-specific antibodies (DSA MFI ≥5,000), 36 ABO-incompatible recipients were excluded. The remaining 105 patients were stratified into desensitized (n=55) and non-desensitized (n=50) groups. By immunological risk category, 52 patients were classified as high risk, 38 as intermediate risk, and 15 as low risk.

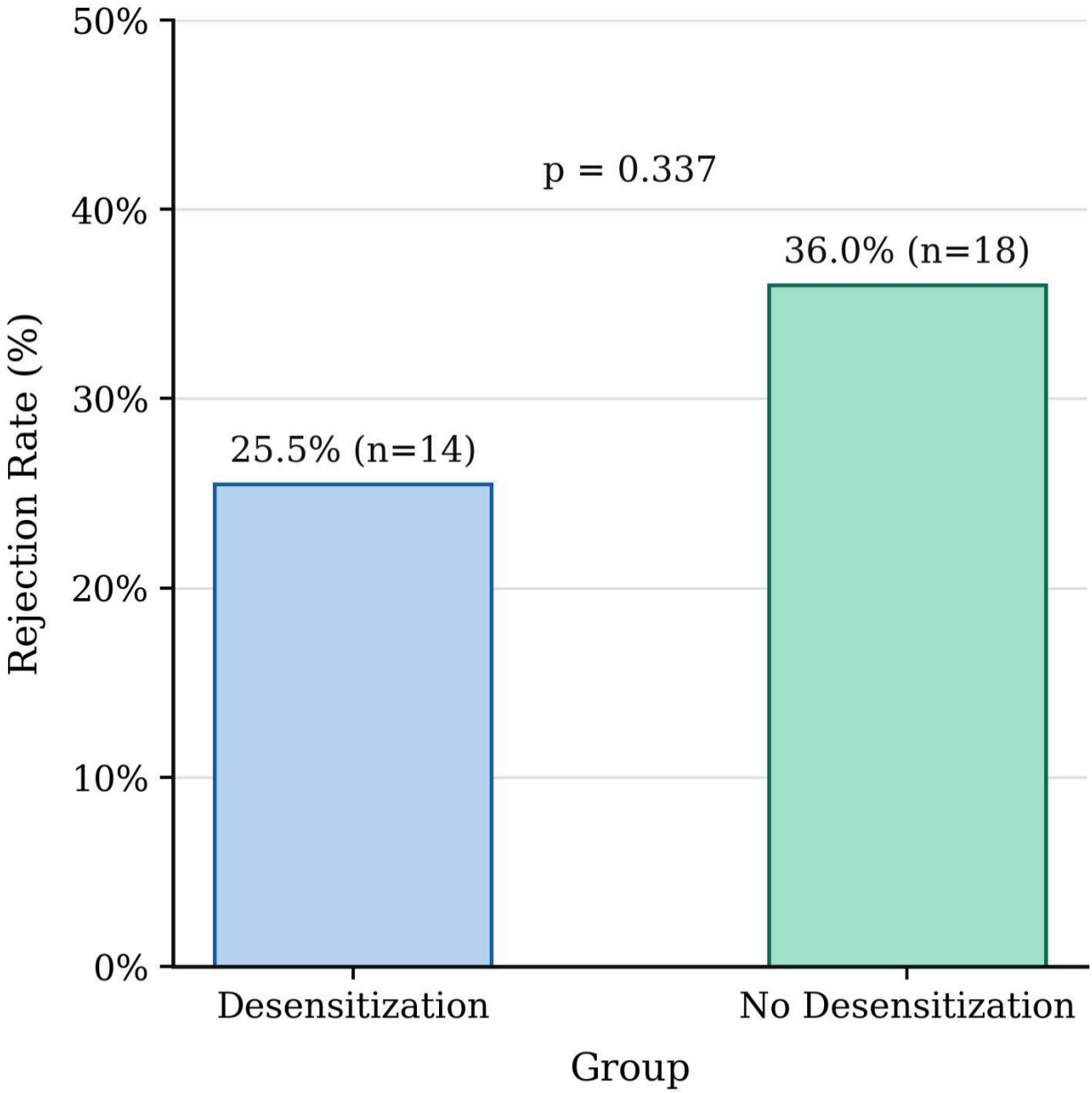


FIGURE 3. Rejection rate by desensitization status. The crude rejection rate was lower in desensitized recipients compared with non-desensitized recipients (25.5% [n=14/55] vs. 36.0% [n=18/50]; p = 0.337). Numbers above bars indicate the rejection rate and the number of events.

Figure 3

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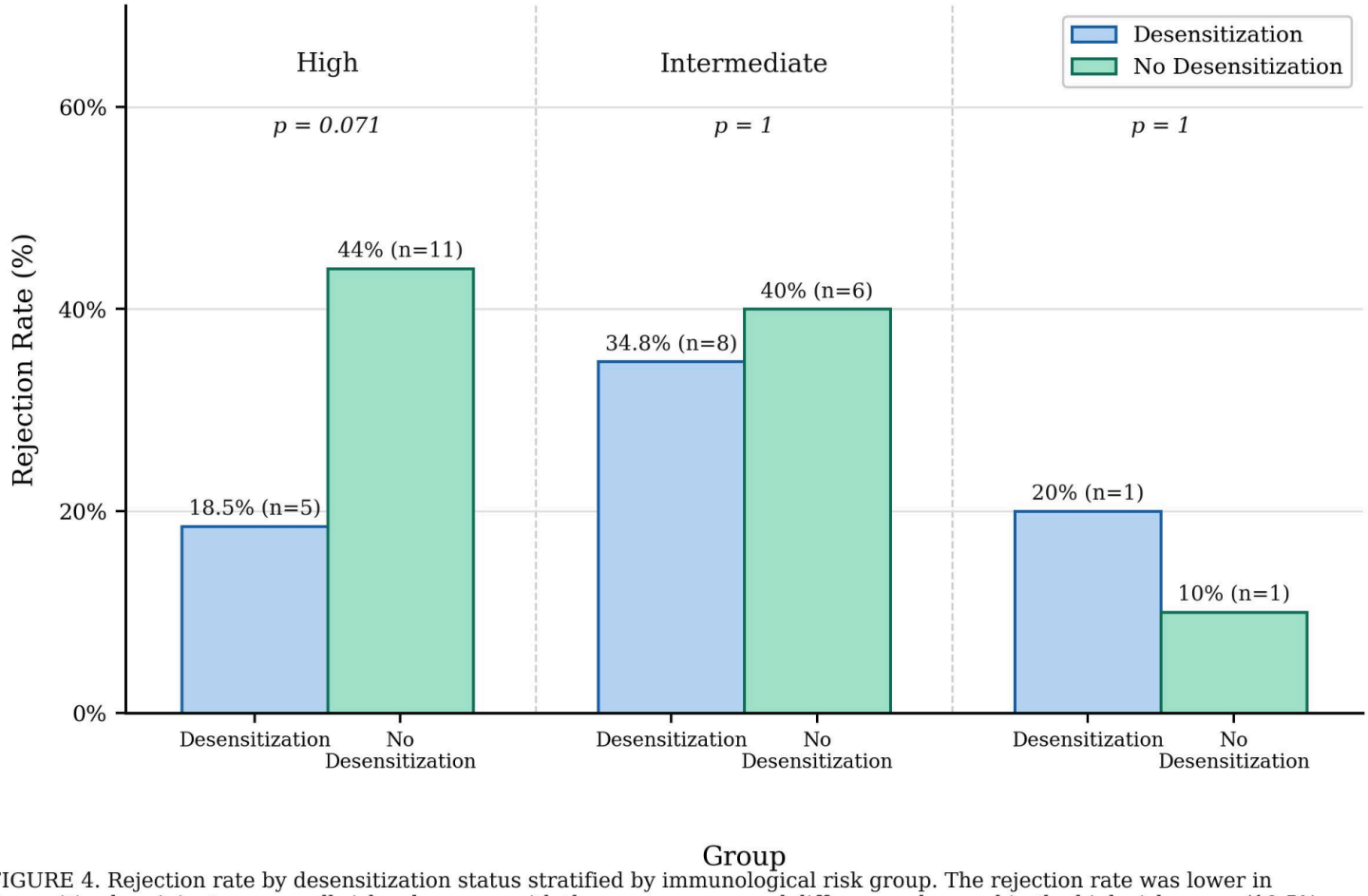


FIGURE 4. Rejection rate by desensitization status stratified by immunological risk group. The rejection rate was lower in desensitized recipients across all risk subgroups, with the most pronounced difference observed in the high-risk group (18.5% [n=5/27] vs. 44.0% [n=11/25]; p = 0.071). In the intermediate- and low-risk groups, rejection rates were comparable between desensitized and non-desensitized recipients (34.8% vs. 40.0%, p = 1; 20.0% vs. 10.0%, p = 1, respectively). Numbers above bars indicate the rejection rate and the number of events.

Figure 4

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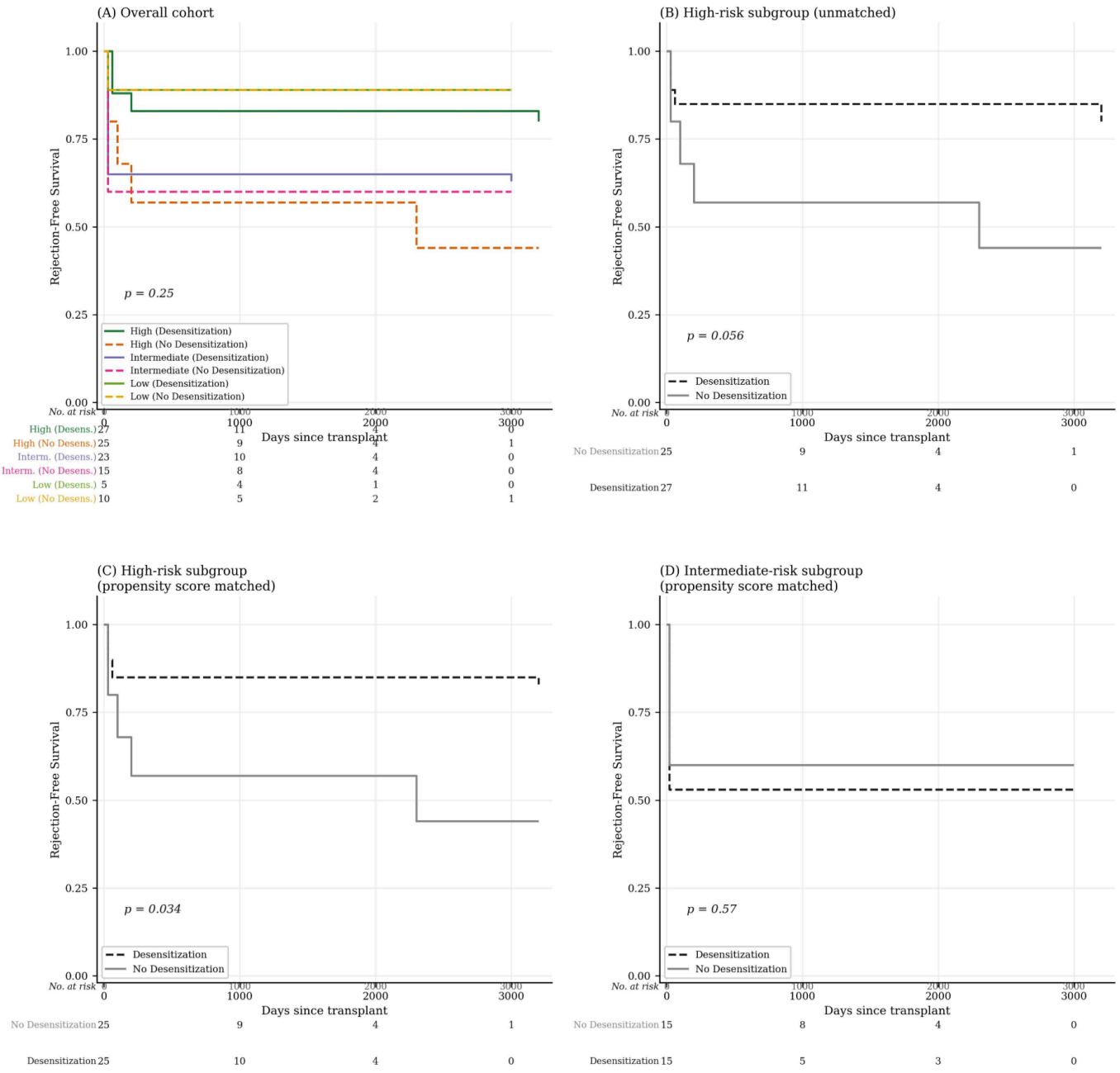


FIGURE 5. Kaplan–Meier curves for rejection-free survival (RFS) by desensitization status. (A) Overall cohort stratified by immunological risk group; solid lines represent No Desensitization and dashed lines represent Desensitization (log-rank p = 0.25). (B) High-risk subgroup (unmatched cohort); desensitized recipients demonstrated a trend toward improved RFS compared with non-desensitized recipients (p = 0.056). (C) High-risk subgroup following propensity score matching; desensitization was associated with significantly improved RFS (p = 0.034). (D) Intermediate-risk subgroup following propensity score matching; no significant difference in RFS was observed between groups (p = 0.57). Tick marks indicate censored observations. Numbers below each panel represent patients at risk at each time point.

Figure 5

See image above for figure legend.

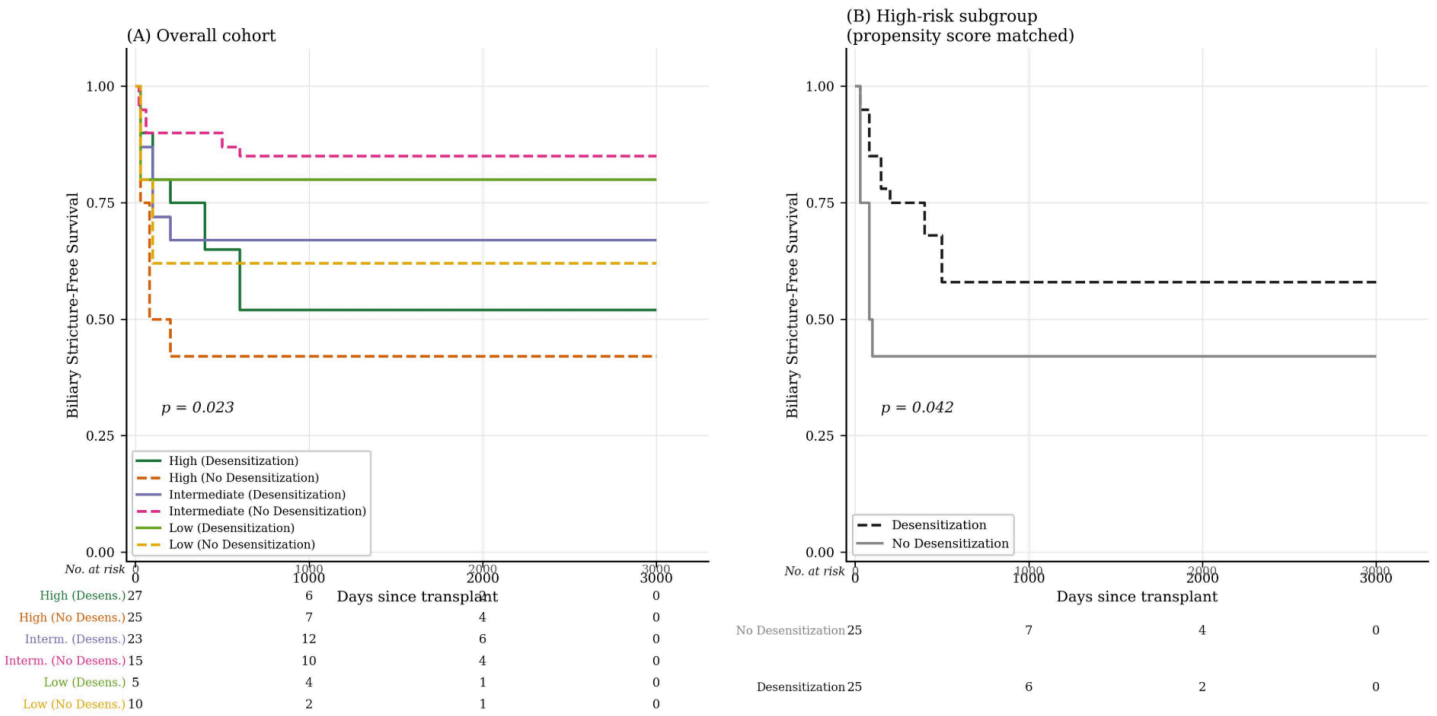


FIGURE 6. Kaplan–Meier curves for biliary stricture-free survival by desensitization status. (A) Overall cohort stratified by immunological risk group; solid lines represent Desensitization and dashed lines represent No Desensitization (log-rank p = 0.023). (B) High-risk subgroup following propensity score matching; desensitization was associated with significantly improved biliary stricture-free survival compared with non-desensitized recipients (p = 0.042), suggesting that immune-mediated biliary injury may be attenuated by perioperative desensitization. Numbers below each panel represent patients at risk at each time point.

Figure 6

See image above for figure legend.

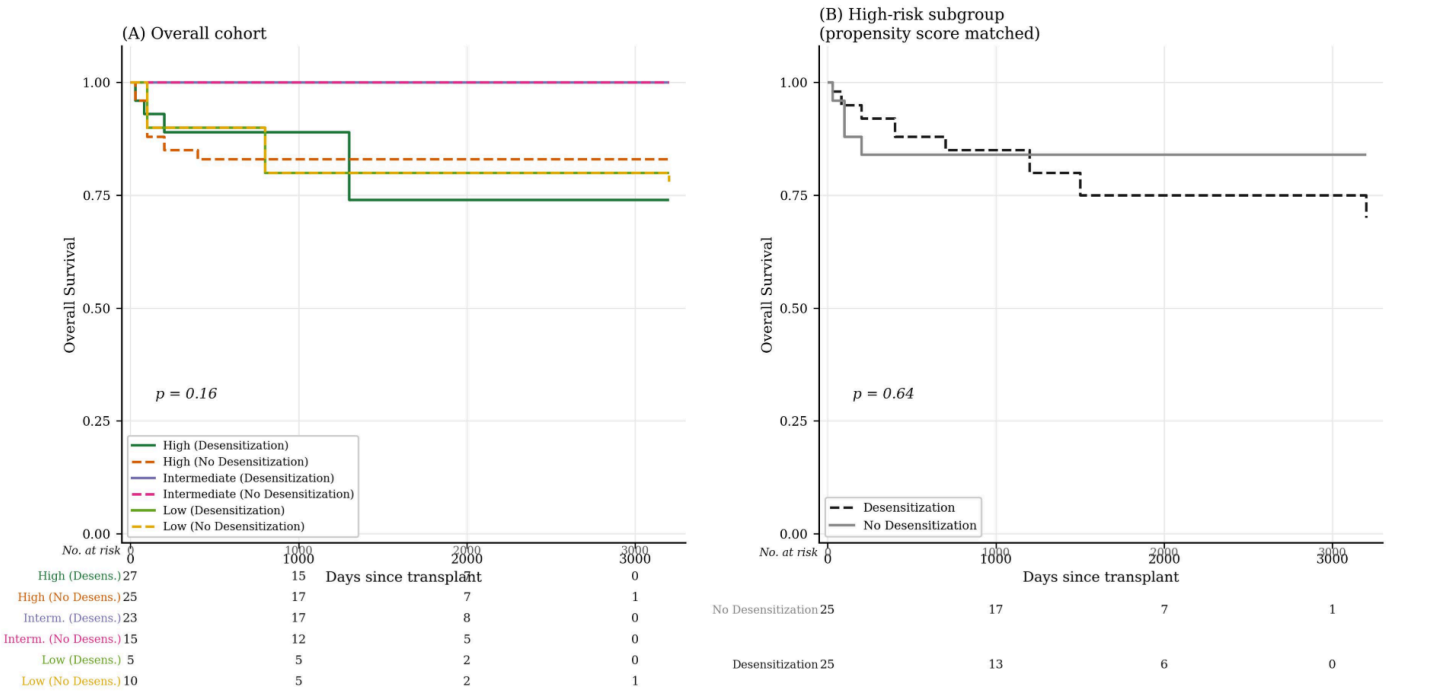


FIGURE 7. Kaplan–Meier curves for overall survival (OS) by desensitization status. (A) Overall cohort stratified by immunological risk group; solid lines represent Desensitization and dashed lines represent No Desensitization (log-rank p = 0.16). (B) High-risk subgroup following propensity score matching; no significant difference in OS was observed between desensitized and non-desensitized recipients (p = 0.64). Desensitization was not associated with a significant improvement in overall survival in either the overall cohort or in the matched high-risk subgroup. Numbers below each panel represent patients at risk at each time point.

Figure 7

See image above for figure legend.

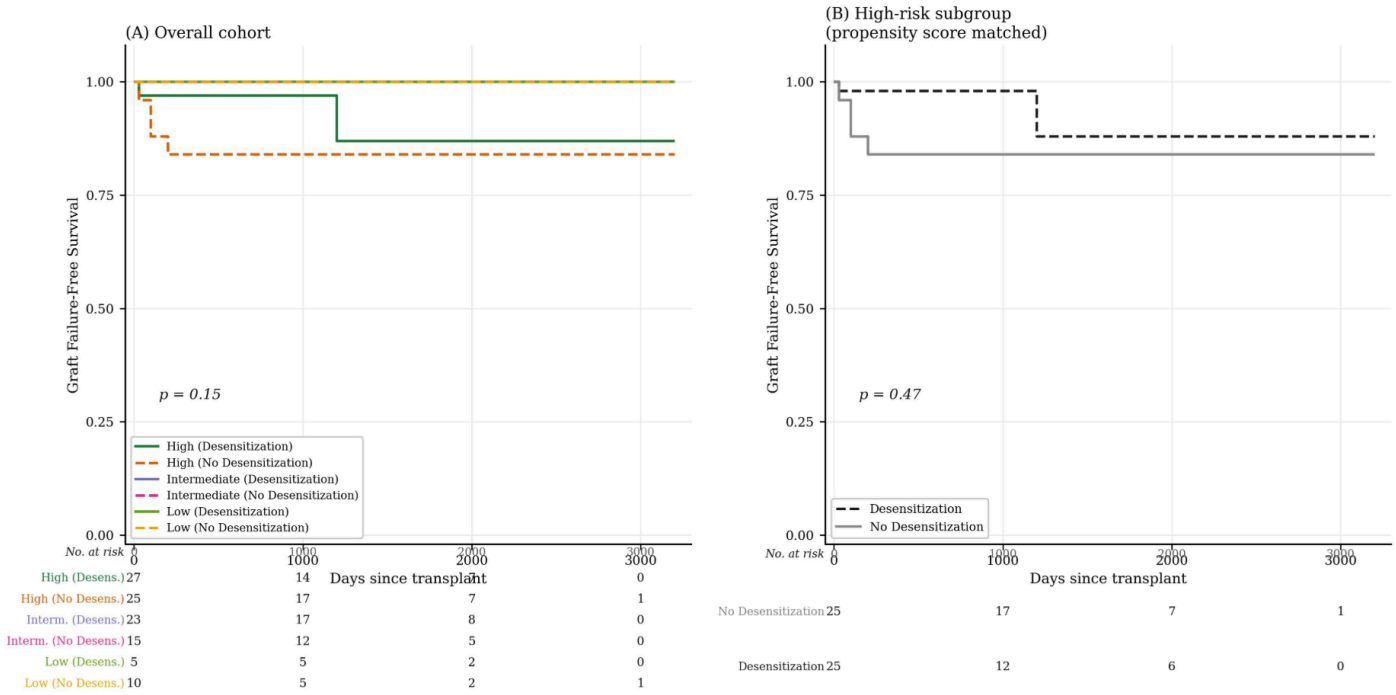


FIGURE 8. Kaplan–Meier curves for graft failure–free survival (GFFS) by desensitization status. (A) Overall cohort stratified by immunological risk group; solid lines represent Desensitization and dashed lines represent No Desensitization (log-rank p = 0.15). (B) High-risk subgroup following propensity score matching; no significant difference in GFFS was observed between desensitized and non-desensitized recipients (p = 0.47). Desensitization was not associated with a significant improvement in graft failure–free survival in either the overall cohort or in the matched high-risk subgroup. Numbers below each panel represent patients at risk at each time point.

Figure 8

See image above for figure legend.