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ORIGINAL ARTICLE

Impact of Share 35 liver transplantation allocation in Australia and New Zealand

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Abstract

Patients with high model for end-stage liver disease (MELD) scores waiting for liver transplantation in Australia and New Zealand (ANZ) have had limited access to deceased donor livers and therefore binational sharing of livers, for patients with a MELD score ≥35 was introduced in February 2016. Waiting list mortality, post-transplant outcomes and intention-to-treat survival were compared between patients whose MELD score reached 35 on the waiting list between October 2013 and April 2015 (Pre-Share 35 group, $n = 23$) and patients who were Share 35 listed between February 2016 and May 2022 (Share 35 group, $n = 112$). There was significantly

reduced waiting list mortality in share 35 listed patients in comparison to the pre-Share 35 group (11.7% vs. 52.2%, OR .120 95% CI .044–.328, $P < .001$). Post-transplant patient and graft survival were not significantly different between the groups (5-year patient survival 82% vs. 84%, $P = .991$, 5-year graft survival 82% vs. 76%, $P = .543$). Intention-to-treat survival was superior in the Share 35 group (HR .302, 95% CI .149–.614, $P < .001$). Introduction of Share 35 in ANZ resulted in a 78% risk reduction in waiting list mortality, equivalent post-transplant survival and an improvement in intention-to-treat survival.

KEYWORDS
end stage liver disease, graft survival, mortality, survival, waiting lists

1 | INTRODUCTION

Liver transplantation relies on a scarce resource and therefore allocation must be underpinned by the ethical principles of equity and utility. An equitable allocation policy ensures even distribution of risk across the waiting list and utility implies satisfactory post-transplant outcomes.

Because of the sparce population distribution and large land area of Australia and New Zealand (ANZ), each of the six liver transplant units has a corresponding donor procurement area that is, on average, larger than the area of Western Europe and more than 1.5 times the average area of the Organ Procurement and Transplantation Network regions in the USA. The five procurement areas in Australia are state- and territory- based (Queensland, New South Wales and the Australian Capital Territory, Victoria and Tasmania, South Australia and the Northern Territory, and Western Australia), whilst New Zealand is a single procurement region.[1] In the absence of urgently listed patients in ANZ, each unit determines the allocation of donor livers in its procurement area to patients on their own list (center-based allocation), based on agreed Transplantation Society of ANZ (TSANZ) allocation guidelines that are underpinned by the "sickest first" principle, guided by model for end-stage liver disease (MELD) score.[1,2]

The liver transplant units in ANZ have a long history of collaboration and organ sharing. In particular, a system of sharing of deceased donor livers between the liver transplant units in ANZ for patients with an urgent need for liver transplantation has been in place for many years.[2] Category 1 patients are those suitable for transplantation with acute liver failure who are ventilated. Allocation of deceased donor livers from any unit in ANZ is mandated. Category 2 patients include those with acute liver failure, meeting King's College criteria, who are not ventilated, children with acute or chronic liver failure who are in a pediatric ICU, children with severe metabolic disorders or hepatoblastoma for whom a limited time period exists where transplantation is possible and patients waiting for combined liver-intestine transplantation. When a donor liver becomes available, discussion occurs between the unit with the category 2 listed patient and the local retrieving unit to determine optimal allocation. This allocation policy has resulted in low waiting list mortality and excellent post-transplant survival for these patients.[3,4] However, patients with chronic liver disease and high MELD scores, who are ineligible as urgent patients since they do not fulfil the above criteria, may be less well served by a single organ donor region, even when allocation occurs to patients with the highest MELD score.[5] Patients with chronic liver disease and high MELD scores on liver transplant waiting lists in ANZ have substantial waiting list mortality rates and could benefit from a system of organ sharing between units.

A retrospective analysis of waiting list mortality in the Victorian Liver Transplant Unit from 2004 to 2008 revealed a waiting list mortality of 38% and a median time to waiting list mortality of 14 days among patients whose MELD score reached 25 or more.[6] Following presentation of these data to the then Liver Transplant Advisory Committee of TSANZ, the peak body that develops liver transplantation guidelines and monitors allocation in the countries, it was agreed to determine the feasibility and likely impact of sharing of deceased donor livers for waiting list patients with various MELD thresholds. Prospective data were collected by the ANZ liver transplant units on patients whose MELD score reached 25 at any time while on the waiting list between October 1, 2013 and April 30, 2015 and simulation of inter-regional sharing models was undertaken and evaluated.[6] This enabled Liver and Intestinal Transplant Advisory Committee (LITAC) members to consider the implications, in terms of numbers of shipped livers, potential waiting list mortality prevented and logistical outcomes, including shipping distance and cold ischemia time, of different scenarios. It was found that setting a MELD threshold of 35 and a difference of at least 10 MELD points between the potential recipient and the sickest patient on the waiting list of the unit with the donor, would result in 21 livers being shipped to potentially save eight patients during the study period and this would require a total of 3563 min of additional cold ischemia time and 32 858 km additional transport distance. Following presentation of the results of the simulations, LITAC agreed to implement sharing of deceased donor livers across ANZ for patients whose MELD score (original, without inclusion of serum sodium) was at least 35. Sharing is discretionary and the unit in whose procurement region a donor is available is not expected to share a liver if there is a suitable patient on the unit's list with a MELD score of 25 or more. To the authors' knowledge, this study describes the sharing of deceased donor livers for

high MELD patients over a greater geographical extent than previously reported.

2 | METHODS

2.1 | Patient groups and analyses

The study groups are the Pre-Share 35 group, consisting of patients listed for liver transplantation in ANZ between October 1, 2013 and April 30, 2015 whose MELD score reached 35 at any time while on the waiting list and the Share 35 group, consisting of patients listed as Share 35 between February 1, 2016 and May 31, 2022. Data were supplied by the Australia and New Zealand Liver and Intestinal Transplant Registry and by the liver transplant units. It was not feasible to include cases in the Pre-Share 35 group earlier than the commencement of prospective data collection because the Registry collects data only at listing and transplantation and does not collect blood test results during the waiting list period. Baseline characteristics, including demographic factors, diseases, MELD scores and the blood tests that comprise MELD score were compared between the groups. Waiting list mortality (including patients who were delisted and died within 1 year) was compared between the groups. In order to determine whether there was any detrimental effect on the rest of the waiting list by diverting donor livers to Share 35 listed patients, waiting list mortality was compared between patients whose MELD did not reach 35 during the Pre-Share 35 period and patients on the waiting list during the Share 35 period who were not Share 35 listed. Post-transplant patient and graft survival were compared between the Pre-Share 35 and Share 35 groups. The groups were also compared with respect to intention-to-treat survival, which is survival after reaching MELD 35 on the waiting list in the Pre-Share 35 group and survival after Share 35 listing in the Share 35 group. This includes both the period of time on the waiting list and after transplantation, for those who were transplanted.

Interim analyses were conducted and presented to LITAC at 6 monthly intervals. The research was conducted in accordance with the Declarations of Helsinki and Istanbul and the Revised Standards for Quality Improvement Reporting Excellence (SQUIRE 2.0). Institutional ethics approval for this study was provided by the Austin Health Human Ethics Review Committee (HREC/89881/Austin-2022) and the study was also approved by LITAC. Written informed consent was obtained for inclusion of data in the Australia and New Zealand Liver and Intestinal Transplant Registry but the need for specific consent for this retrospective analysis was waived. No donor organs were obtained from executed prisoners.

2.2 | Statistics

Categorical data are presented as number (%) and were compared using the Pearson chi square test. Normality of distribution of continuous variables was assessed using the Shapiro-Wilk test. Normally distributed data are presented as mean ± standard deviation and were compared using the *t*-test. Non-normally distributed data are presented as median (interquartile range [IQR]) and were compared using the Mann-Whitney *U* test. Risk factors for waiting list mortality were assessed using univariable binary logistic analysis. Factors with a *P* value < .1 were entered into multivariable binary logistic regression. In order to control for the effects of the introduction of direct-acting antiviral medications around the time of commencement of the Share 35 policy, a separate analysis of waiting list mortality excluding patients with hepatitis C virus (HCV) cirrhosis was undertaken. Risk factors for post-transplant mortality and graft loss were assessed using univariable Cox proportional hazards analysis. Factors with a *P* value < .1 were entered into multivariable Cox proportional hazards regression. Survival analyses included post-listing survival (time from reaching MELD 35 in the Pre-Share 35 group and time from listing as Share 35 in the Share 35 group to death or end of follow-up, with end of follow-up censored and death uncensored), post-transplant patient survival (transplant date to death or end of follow-up, with end of follow-up censored and death uncensored) and post-transplant graft survival (transplant date to retransplantation or to death in patients who were not retransplanted or to end of follow-up in patients who were not retransplanted and who had not died, with end of follow-up censored and retransplantation and death uncensored). Kaplan-Meier survival curves were generated and groups were compared using the log-rank test. Statistical analysis was undertaken using IBM SPSS Statistics, version 27. *P* values < .05 were considered significant.

3 | RESULTS

3.1 | Baseline characteristics

There were 23 patients in the Pre-Share 35 group and 111 patients who had 112 listings (one patient who underwent transplantation as a Share 35 patient was listed for retransplantation as a Share 35 patient) in the Share 35 group. No patient in either group was lost to follow-up and there were no missing datapoints in the variables that were assessed. During the Share 35 period (February 1, 2016–May 31, 2022), 32 patients who were not Share 35 listed had a delisting MELD score ≥35, none of whom were transplanted and all but four of whom died, indicating that transplantation was considered futile in the majority of these patients. The baseline characteristics of the Pre-Share 35 and Share 35 groups are listed in Table 1. In comparison to the Pre-Share 35 group at the time their MELD score reached at least 35, the Share 35 group at the time of Share 35 listing had a lower proportion of patients with hepatitis C virus (10.7% vs. 30.4%, $P = .01$) and a higher mean bilirubin level (505 ± 228 vs. 373 ± 210 μmol/L, $P = .01$).

Eleven (47.8%) of the Pre-Share 35 patients and 99 (88.4%) of the Share 35 patients were transplanted. At transplantation, in comparison to the Pre-Share 35 group, the Share 35 group had a shorter wait to transplantation (5 days, IQR 2-10 vs. 17 days, IQR 9-26, $P < .001$), were less likely to be non-urgent at the time of transplantation (14.1% vs. 100%, $P < .001$) and more likely to be Share 35 at transplantation

TABLE 1 Baseline characteristics of Pre-Share 35 and Share 35 listings. Data are displayed as mean ± SD, median (IQR) or *n* (%). Data are measured at date MELD ≥35 for the Pre-Share 35 group and at Share 35 listing for the Share 35 group and at transplant for both groups. Variables with *P* value < .05 shown in bold.

	At MELD 35 or Share 35			At transplant		
Variable	**Pre-Share 35**	**Share 35**	**P value**	**Pre-Share 35**	**Share 35**	***P* value**
N	23	112		11	99	
Sex (male)	18 (78.3%)	66 (58.9%)	.08	9 (81.8%)	58 (58.6%)	.13
Age (years)	55 (47–61)	51 (40–57)	.10	55 (44–64)	51 (38–56)	.21
Previous liver transplant	2 (8.7%)	22 (19.6%)	.21	1 (9.1%)	19 (19.2%)	.41
Disease[a]						
Alcohol	4 (17.4%)	31 (27.7%)	.30	2 (18.2%)	29 (29.3%)	.44
Cholestatic	4 (17.4%)	18 (16.1%)	.88	3 (27.3%)	16 (16.2%)	.36
FHF or subacute	1 (4.3%)	11 (9.8%)	.40	0 (0%)	9 (9.1%)	.30
HBV	5 (21.7%)	12 (10.7%)	.15	2 (18.2%)	11 (11.1%)	.49
HCC	2 (8.7%)	9 (8.0%)	.92	1 (9.1%)	7 (7.1%)	.81
HCV	**7 (30.4%)**	**12 (10.7%)**	**.01**	2 (18.2%)	9 (9.1%)	.34
Metabolic	0 (0%)	12 (10.7%)	.10	0 (.0%)	11 (11.1%)	.24
NAFLD	3 (13.0%)	16 (14.3%)	.88	1 (9.1%)	14 (14.1%)	.64
Other	4 (17.4%)	22 (19.6%)	.80	2 (18.2%)	19 (19.2%)	.94
Blood group						
A	7 (30.4%)	36 (32.1%)	.87	4 (36.4%)	31 (31.3%)	.73
AB	1 (4.3%)	4 (3.6%)	.86	0 (0%)	3 (3.0%)	.56
B	5 (21.7%)	24 (21.4%)	.87	1 (9.1%)	21 (21.2%)	.34
O	10 (43.5%)	48 (42.9%)	.96	6 (54.5%)	44 (44.4%)	.52
Creatinine (μmol/L)	222 (112–304)	153 (111–222)	.06	149 (108–180)	117 (83–193)	.61
Bilirubin (μmol/L)	**373 ± 210**	**505 ± 228**	**.01**	410 ± 244	507 ± 234	.23
INR	2.9 (2.5–3.9)	2.9 (2.3–3.8)	.81	2.3 (1.9–2.6)	2.5 (1.9–3.7)	.30
MELD score	36 (35–41)	37 (35–40)	.80	32 (28–34)	35 (32–38)	.06
Delta MELD[b]				−4.2 ± 4.6	−2.6 ± 5.8	.32
Time to transplant (days)[c]				**17 (9–26)**	**5 (2–10)**	**<.001**
Urgency						
Non-urgent				**11 (100%)**	**14 (14.1%)**	**<.001**
Share 35				**0 (0%)**	**80 (80.8%)**	**<.001**
Category 2				0 (0%)	3 (3.0%)	.56
Category 1				0 (0%)	2 (2.0%)	.63
Medical condition						
Home				**2 (18.2%)**	**3 (3.0%)**	**.02**
Hospital				7 (63.6%)	63 (63.6%)	>.99
ICU				11 (9.1%)	21 (21.2%)	.34
Ventilated				1 (9.1%)	12 (12.1%)	.77
Donor						
Age (years)				51 (42–56)	42 (26–59)	.34
Height (cm)				173 (162–185)	170 (164–180)	.45
Cause of death						
Trauma				2 (18.2%)	18 (18.2%	>.99

(Continues)

TABLE 1 (Continued)

	At MELD 35 or Share 35			At transplant		
Variable	**Pre-Share 35**	**Share 35**	**P value**	**Pre-Share 35**	**Share 35**	***P* value**
Stroke				6 (54.5%)	47 (47.5%)	.66
Anoxia				3 (27.3 %)	31 (31.3%)	.78
Other				0 (0%)	3 (3.0%)	.56
DCD				0 (0%)	9 (9.1%)	.30
Ethnicity						
White				11 (100%)	85 (85.9%)	.18
Asian				0 (0%)	9 (9.1%)	.30
Indigenous or Islander				0 (0%)	5 (5.1%)	.45
DRI				**1.40 (1.19–1.59)**	**1.61 (1.36–1.98)**	**.04**
Transplant						
CIT (mins)				337 (312–438)	385 (300–501)	.22
Distance (km)[d]				**19 (16–117)**	**658 (12–806)**	**.047**
ABO compatibility						
Identical				**10 (90.9%)**	**58 (58.6%)**	**.04**
Compatible				1 (9.1%)	33 (33.3%)	.10
Incompatible (donor A2)				0 (0%)	5 (5.1%)	.45
Incompatible				0 (0%)	3 (3.0%)	.56
Graft type						
Whole				11 (100%)	89 (89.9%)	.27
Split				0 (0%)	8 (8.1%)	.33
Reduced				0 (0%)	2 (2.0%)	.63

Abbreviations: CIT, cold ischemia time; DCD, donation after circulatory death; DRI, donor risk index; FHF, fulminant hepatic failure; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ICU, intensive care unit; INR, international normalized ratio; MELD, model for end-stage liver disease; NAFLD, non-alcoholic fatty liver disease.

[a]Disease included in any of up to four recorded for each patient, hence numbers add to more than number of patients.

[b]MELD at transplant minus MELD at Share 35 listing.

[c]Time from Share 35 listing to transplant.

[d]Distance between donor and recipient hospital, calculated using spherical law of cosines (great circle).

(80.8% vs. 0%, $P < .001$), as expected, were less likely to be at home prior to transplantation (3.0% vs. 18.2%, $P = .02$), had a higher donor risk index (1.61, IQR 1.36–1.98 vs. 1.40, IQR 1.19–1.59, $P = .04$), a greater distance between donor and recipient hospitals (658 km, IQR 12–806 vs. 19 km, IQR 16–117, $P = .047$) and were less likely to have an ABO-identical transplant (58.6% vs. 90.9%, $P = .04$). The other baseline characteristics at MELD 35 and at transplantation were not significantly different between the groups.

3.2 | Waiting list mortality

Of the 23 Pre-Share 35 listed patients, 12 died waiting and 11 were transplanted. Of the 111 patients who were Share 35 listed, 13 died waiting (including the patient who was Share 35 listed after being transplanted as a Share 35 patient) and 99 were transplanted. There was a significantly reduced waiting list mortality in Share 35 listed patients in comparison to the Pre-Share 35 group (11.7% vs. 52.2%, respectively, OR .120 95% CI .044–.328, $P < .001$, Table 2). Waiting list mortality was higher with increasing age (OR 1.046, 95% CI 1.004–1.090, $P = .03$), in patients with hepatitis C virus (HCV) cirrhosis than other indications (OR 4.235, 95% CI 1.488–12.055, $P = .007$) and with increasing MELD score (OR 1.115, 95% CI 1.002–1.241, $P = .046$). Group and MELD score were also significant on multivariable analysis of waiting list mortality risk factors (Share 35: OR .140, 95% CI .047–.410, $P < .001$; MELD score: OR 1.152, 95% CI 1.021–1.301, $P = .02$). The median time from MELD ≥35 to waiting list death was 8 days (IQR 2-20) in the Pre-Share 35 group and 5 days (IQR 2–14) in the Share 35 group ($P = .538$). Excluding patients with HCV, there were 16 Pre-Share 35 listed patients, of whom 7 (44%) died waiting and 101 Share 35 listed patients, of whom 10 (10%) died waiting (Share 35 OR .141, 95% CI .0432–.462, $P < .001$).

There were 707 patients wait listed during the Pre-Share 35 period whose MELD score did not reach 35 and 2437 patients wait listed during the Share 35 period who were not Share 35 listed. Among these patients, waiting list mortality was lower in the Share 35 period

TABLE 2 Univariable and multivariable binary logistic regression analysis of factors associated with waiting list mortality. Variables with *P* value < .05 shown in bold.

	Univariable			Multivariable		
Variable	**OR**	**95% CI**	**P value**	**OR**	**95% CI**	***P* value**
Group (Share 35)	**.120**	**.044–.328**	**< .001**	**.140**	**.047–.410**	**<.001**
Sex (male)	1.364	.542–3.434	.51			
Age (years)	**1.046**	**1.004–1.090**	**.03**	1.036	.988–1.085	.14
Previous liver transplant	.974	.298–3.176	.97			
Disease						
Alcohol	.485	.154–1.529	.22			
Cholestatic	.653	.177–2.405	.52			
FHF or subacute	1.547	.383–6.117	.55			
HBV	1.421	.421–4.794	.57			
HCC	1.739	.427–7.083	.44			
HCV	**4.235**	**1.488–12.055**	**.007**	3.178	.972–10.387	.06
Metabolic	.375	.046–3.047	.36			
NAFLD	1.206	.363–4.005	.76			
Other	1.060	.356–3.149	.92			
Blood group						
A	1.008	.397–2.559	.99			
AB	3.101	.490–19.627	.23			
B	1.556	.578–4.187	.38			
O	.565	.225–1.417	.22			
Creatinine (μmol/L)	1.003	.999–1.006	.11			
Bilirubin (μmol/L)	1.000	.998–1.002	.77			
INR	1.095	.856–1.399	.47			
MELD	**1.115**	**1.002–1.241**	**.046**	**1.152**	**1.021–1.301**	**.02**

Abbreviations: CI, confidence interval; FHF, fulminant hepatic failure; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; INR, international normalized ratio; MELD, model for end-stage liver disease; NAFLD, non-alcoholic fatty liver disease; OR, odds ratio.

(Pre-Share 35 period 10.6% vs. Share 35 period 6.0%, Share 35 period: OR .537, 95% CI .401–.719, *P* < .001).

3.3 | Post-transplant survival

Post-transplant patient and graft survival were not significantly different between the Pre-Share 35 and Share 35 groups (Figure 1). One-, 3- and 5-year patient survival was 91%, 91%, and 82%, respectively in the Pre-Share 35 group and 91%, 88%, and 84%, respectively in the Share 35 group (*P* = .99). One-, 3- and 5- year graft survival was 91%, 91% and 82%, respectively in the Pre-Share 35 group and 84%, 80% and 76% in the Share 35 group (*P* = .54).

3.4 | Intention-to-treat survival

The median follow-up time in the Pre-Share 35 group was 7.9 years and in the Share 35 group was 2.3 years. The median survival time in the Pre-Share 35 group was 1.1 years and in the Share 35 group was not reached. There were 16 (59%) deaths in the Pre-Share 35 group and 24 (22%) deaths in the Share 35 group (*P* < .001). Intention-to-treat analysis revealed that survival after MELD 35 on the waiting list (including both waiting list and post-transplant periods) was superior in the Share 35 group (Figure 1). One-, 3- and 5-year survival was 52%, 44%, and 39%, respectively in the Pre-Share 35 group and 80%, 78%, and 74%, respectively in the Share 35 group (*P* < .001). Univariable Cox proportional hazards analysis revealed that Share 35 listing (HR .309, 95% CI .160–.598, *P* < .001) and alcohol-related cirrhosis (HR .308, 95% CI .109–.866, *P* = .03) were associated with a reduced risk of intention-to-treat mortality and HCV cirrhosis (HR 2.232, 95% CI 1.056–4.716, *P* = .04) and MELD score (HR 1.075, 95% CI 1.003–1.152, *P* = .04) were associated with an increased risk of intention-to-treat mortality (Table 3). In addition, mortality was higher in patients who had previously undergone liver transplantation (HR 1.870, 95% CI .909–3.846, *P* = .09), although this difference was not statistically significant on univariable analysis. Four of the five factors were significant on multivariable Cox proportional hazards regression (Share 35: HR .302, 95%

TABLE 3 Univariable and multivariable Cox proportional hazards regression analysis of factors associated with intention-to-treat mortality. Variables with *P* value < .05 shown in bold.

	Univariable			Multivariable		
Variable	**HR**	**95% CI**	**P value**	**HR**	**95% CI**	**P value**
Group (Share 35)	**.309**	**.160–.598**	**<.001**	**.302**	**.149–.615**	**<.001**
Sex (male)	1.140	.593–2.194	.69			
Age (years)	1.019	.994–1.044	.13			
Previous liver transplant	1.870	.909–3.846	.09	**2.443**	**1.118–5.340**	**.02**
Disease						
Alcohol	**.308**	**.109–.866**	**.03**	.406	.137–1.199	.10
Cholestatic	1.173	.517–2.661	.70			
FHF or subacute	.829	.255–2.692	.78			
HBV	1.048	.409–2.686	.92			
HCC	1.490	.529–4.197	.45			
HCV	**2.232**	**1.056–4.716**	**.04**	**2.421**	**1.095–5.351**	**.03**
Metabolic	.553	.133–2.297	.42			
NAFLD	.908	.355–2.323	.84			
Other	1.523	.758–3.060	.24			
Blood group						
A	.812	.403–1.633	.56			
AB	1.522	.366–5.936	.84			
B	1.328	.647–2.725	.44			
O	.908	.478–1.724	.77			
Creatinine (μmol/L)	1.001	.999–1.003	.16			
Bilirubin (μmol/L)	1.000	.999–1.001	.99			
INR	.975	.809–1.174	.79			
MELD	**1.075**	**1.003–1.152**	**.04**	**1.112**	**1.032–1.200**	**.006**

Abbreviations: CI, confidence interval; FHF, fulminant hepatic failure; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; INR, international normalized ratio; MELD, model for end-stage liver disease; NAFLD, non-alcoholic fatty liver disease.

CI .149–.615, *P* < .001; previous liver transplant: HR 2.443, 95% CI 1.118–5.340, *P* = .02; HCV cirrhosis: HR 2.421, 95% CI 1.095–5.351, *P* = .03 and MELD score: HR 1.112, 95% CI 1.032–1.200, *P* = .006).

4 | DISCUSSION

Patients who were listed as Share 35 had a 78% risk reduction in waiting list mortality in comparison to a similar group of waiting list patients whose MELD score reached 35 while they were on the waiting list prior to the institution of the Share 35 program. Being listed as a Share 35 patient was independently associated with a reduction in waiting list mortality.

Patients in the USA with chronic liver disease and a MELD score >35 were shown to have a waiting list mortality approximating or exceeding that of status 1A patients and had limited access to deceased donor livers.[7] In response to inequities in the allocation system in the USA and after simulation of the expected impacts of changes in allocation policy, in June 2013, the United Network for Organ Sharing implemented the Share 35 allocation system, which prioritizes for transplantation patients in an organ procurement region with a MELD score ≥35 over local patients with a lower MELD score. Early reports on the effects of Share 35 revealed increased access to transplantation for patients with a MELD score ≥35,[8] including reduced waiting time,[9–11] but the impact on waiting list mortality was reported variably.[8,12]

Edwards et al. subsequently reported on the first two years of the Share 35 policy, reporting a 22% reduction in waiting list mortality, from 32% to 25%, in patients with a MELD score ≥35.[13] There was a greater reduction in waiting list mortality in a comparable group of patients in ANZ, partly because the starting point was from a higher waiting list mortality (52.2%) than in the USA but also because the waiting list mortality fell to a lower level (11.7%) than in the USA. The higher initial waiting list mortality likely relates to the smaller population in which each of the ANZ units is based (averaging approximately 4.7 million) and the relatively low deceased donor rate at the time (16.1 per million per year in Australia and 10.2 per million per year in New Zealand, compared with 27.0 per million per year in the USA, in 2014),[14] which result in a limited opportunity for critically ill patients

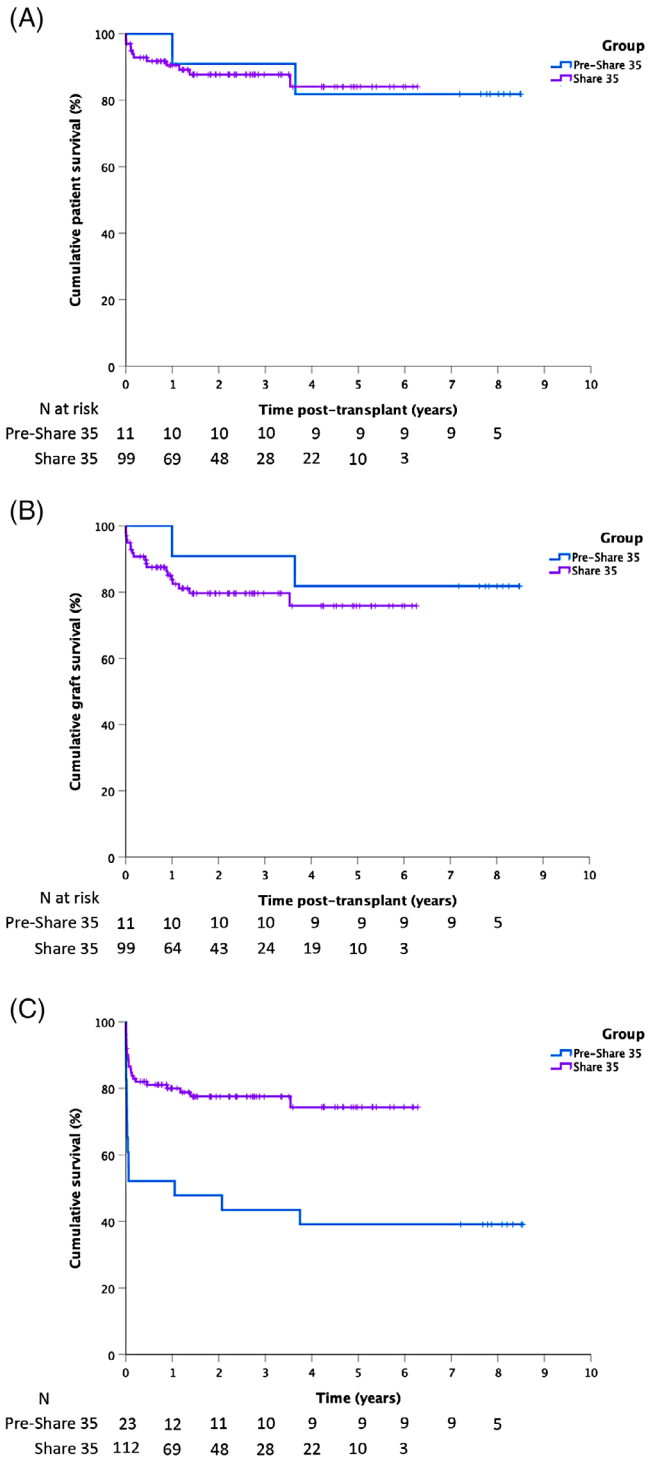

FIGURE 1 Comparison of post-transplant patient (A) and graft (B) survival and intention-to-treat survival (C) between Pre-Share 35 and Share 35 groups.

to access a deceased donor liver during their waiting time. The lower waiting list mortality in ANZ in comparison to the USA after initiation of Share 35 may relate to both a modest increase in deceased donor rates (to 18.0 per million per year in Australia and 12.6 per million per year in New Zealand by 2020, compared with 38.0 per million per year in the USA, in 2020)[15] and sharing of deceased donor livers across all donor regions of both countries. Another factor which may have impacted on waiting list survival is the fact that direct-acting antiviral therapy for HCV, a diagnosis that this study has shown is associated with an increased risk of waiting list mortality, became publicly funded in ANZ from March 2016, which corresponds to the timing of commencement of Share 35 in the countries, although we have shown a reduction in waiting list mortality in patients without HCV cirrhosis.

Sharing of deceased donor livers for waiting list patients with chronic liver disease and high acuity in a region of the United Kingdom (the "UK Northern Alliance", consisting of the centers in Edinburgh, Leeds and Newcastle) resulted in reduced time to transplantation but no difference in waiting list mortality in comparison to similar patients in centers outside this region.[16]

Regional sharing was also introduced in the Lazio region of Italy. Standard criterion donors (<65 years old) are offered to the highest-ranking patient by MELD in the region, whereas extended criteria donors are used locally. Following introduction of regional sharing between the four centers in the Lazio region, there was a reduction in waiting list mortality from 22% to 14%, although the largest reduction was in patients with hepatocellular carcinoma.[17]

In the current study, there was also a reduction in waiting list mortality for patients who were not Share 35 listed. This is likely due to an increase in organ donation rates in ANZ during the study period.[15] There appears to have been no detrimental effect of the Share 35 program on patients who were wait listed but were not Share 35 patients. Similar waiting list outcomes for non-Share 35-listed patients have also been reported in the USA.[8,13] However, a study that analyzed the outcome of "reprioritized" candidates (patients on the local waiting list to whom a deceased donor liver would have been allocated under the previous system but who were passed over for a Share 35 patient in the same region) found that these patients had a 15% rate of waiting list death or delisting due to deterioration.[18] Reprioritized patients whose MELD score was within three of the regional recipient had a 21% rate of waiting list death or delisting due to deterioration. In order to avoid disadvantaging local waiting list patients with a similar MELD score to the potential Share 35 recipient, the agreed approach in ANZ is that a deceased donor liver is not exported to a Share 35 patient if there is a suitable patient on the local waiting list with a MELD score ≥25. It is possible that this policy reduces the opportunity of Share 35 listed patients to access timely transplantation, but this question was not examined in the current study.

Analysis of post-transplant survival of patients transplanted after being listed as Share 35 patients in ANZ revealed good utility, with similar post-transplant patient and graft survival to the pre-Share 35 group. These outcomes are also similar to those for the overall outcomes of liver transplantation in ANZ.[4] Some studies comparing post-transplant patient and graft survival of patients with MELD ≥35 before and after introduction of Share 35 in the USA have also demonstrated similar outcomes,[8,13,19,20] whilst others have shown improved survival in the Share 35 era.[11,21]

The current study found that intention-to-treat survival, which incorporates both waiting list and post-transplant components, was significantly better in the Share 35 group compared with the pre-Share

35 group and Share 35 listing was independently associated with increased intention-to-treat survival. Although the follow-up time was longer in the Pre-Share 35 group, the median survival time of this group was well within the median follow-up time of the Share 35 group, indicating that an adequate follow-up time was achieved. Intention-to-treat survival in relation to Share 35 allocation has not been widely studied previously.

Given the increased cost of shipping organs and an increased transplant rate of sick patients with the potential for a more complicated post-transplant course under Share 35, it might be expected that costs would increase. The costs of transplantation under the Share 35 policy have been examined in several studies. Some have shown increased costs after Share 35 was instituted.[22,23] An increased rate of biliary complications but with no change in post-transplant hospital stay or direct costs has been reported.[24] A single center study from the Mayo clinic found lower 1-year pre-transplant costs and no significant difference in post-transplant costs.[25] Post-transplant morbidity, length of stay and costs were not examined in the current study.

The introduction of Share 35 was undertaken in ANZ only after a period of prospective data collection which formed the basis of simulation of models of organ sharing. These enabled the balancing of the potential benefit to patients who had previously been poorly served by the allocation processes against the costs in terms of increased shipping distance and cold ischemia time. After careful evaluation of the simulation models, Share 35 was introduced and was evaluated 6 monthly by LITAC to ensure that there were no untoward effects. The relatively small liver transplant community meets regularly and has a long history of cooperation, collaboration and organ sharing. These characteristics doubtlessly contributed to the successful implementation of Share 35 in both countries.

This study has some limitations. Any study comparing time periods before and after the introduction of a new policy has the disadvantage of changes occurring other than the policy under review which might confound the outcomes. In particular, the increase in deceased organ donor rates and availability of direct-acting antiviral therapy for HCV during the study period might have contributed to the improved waiting list survival in the Share 35 listed patients. However, waiting list mortality was significantly lower in the Share 35 listed patients even when patients with HCV were excluded. Furthermore, it is clear that the reduction in waiting list mortality of Share 35 listed patients is greater than that experienced by patients who were not listed as Share 35. In order to minimize the risk of extraneous variables contributing to the change in outcome, multivariable analyses were performed that showed that Share 35 listing was independently associated with reduced waiting list mortality and improved intention-to-treat survival. Another limitation is the fact that it was at the discretion of units to list patients as Share 35 and there were patients whose MELD score reached 35 and who were not listed as Share 35 patients. This could particularly apply when it was considered that transplantation was futile and the exclusion of such patients from the Share 35 group could artificially reduce the waiting list mortality in this group.

Patients in ANZ with high MELD scores, who previously had limited access to liver transplantation, have benefited from the introduction of Share 35, with sharing of deceased donor livers across all donor regions of the two countries. This has resulted in a 78% risk reduction in waiting list mortality and equivalent post-transplant survival, while causing no detriment to the general liver transplant waiting list survival.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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