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# **Epidemiology and Comorbidity Burden of Organ Donor Referrals in Australia: Cohort Study** 2010–2015

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**Background.** Increasing organ donation rates in Australia have been exceeded by a rise in potential donor referrals not proceeding to donate. Referral evaluation is resource-intensive. We sought to characterize organ donor referrals in New South Wales, Australia, and identify predictors of referrals not proceeding to donation. **Methods.** We performed a cohort study of NSW Organ and Tissue Donation Service logs 2010–2015, describing the prevalence and impact of comorbidities on referral outcome. Logistic regression was used to identify comorbidities influencing outcome and predict probability of donation. **Results.** Of 2977 referrals, 669 (22%) donated and 2308 (78%) did not. Despite increasing donation rates, the proportion proceeding to donate declined 2010–2015. Among referrals, the prevalence of all comorbidities except cerebrovascular disease increased and was higher among nondonors. History of cardiac disease, >65 years of age, chronic kidney or liver disease, malignancy, and absence of cerebrovascular disease were all significantly (*P* < 0.01) associated with non donation. Hypertension and diabetes did not significantly impact outcome. Predicted probability of donation varied from <1% to 54% depending on comorbidities may significantly impact referral outcome. A better understanding of referral characteristics associated with non donation may improve the efficiency of the referral process in the context of encouraging routine referrals.

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or most people with end-stage organ disease, transplantation is the optimal therapy. The utility of transplantation worldwide is limited by a critical shortage of donor organs. Efforts to increase organ donation rates in Australia resulted in a peak of 18.3 donors per million population in 2015, a significant rise from 15.1 donors per million population in 2011.<sup>1</sup> This improvement was facilitated by increased

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use of the donation after circulatory death pathway and greater consideration of marginal donors based on expanded eligibility criteria,<sup>2,3</sup> as well as increasing referrals of potential organ donors from hospitals.

Initiatives to increase awareness of the organ donor referral process and to assist with recognition of potential organ donors, have contributed significantly to increases in donation

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rates in recent years.<sup>4</sup> However, the increase in total referrals has also increased the proportion of referrals that do not proceed to donation. The labor-intensive nature of processing an organ donation referral has meant that with the growing number of potential organ donors, greater resources are expended on referrals that do not proceed to donation. This is of particular importance in the context of the move towards encouraging routine referrals of all potential organ donors from hospitals for consideration for donation to ensure that no opportunities for donation are overlooked, which will likely increase the volume of referrals further. Identifying referrals unlikely to become donors earlier in the referral pathway, using information readily available from donors' medical histories, may provide scope to improve the efficiency of the donation referral process and focus resources on those referrals most likely to result in donation.

New South Wales is Australia's most populous state, with a population of 7.4 million people, and is demographically representative of the country. The NSW Organ and Tissue Donation Service (OTDS) receives and logs all referrals of possible organ donors from hospitals across the state. Specialist donation staff approach next of kin for consent for donation, and will not proceed with the referral if family consent is declined. Often simultaneously, donation staff may seek advice about medical suitability for donation from a small team of specialist clinicians with expertise in transplantation. Where potential donors are deemed medically unsuitable for donation, the referral does not proceed further.

There are currently no validated indices for predicting organ donor referrals proceeding to donation. Although the Kidney Donor Risk Index (KDRI)<sup>5</sup> is widely used in transplantation medicine to predict the risk of graft failure after kidney transplantation, it was not intended for application in the setting of donor referral evaluation. Ideally, information readily available from referrals' medical histories could be utilized to prioritize those referrals with a greater likelihood of resulting in donation, and identify those unlikely to donate early in the referral process. This would help to ensure that the increase in donor referrals remains sustainable, and continues to contribute to growing organ donation rates in Australia.

The aims of this study were to characterize deceased donor referrals in NSW from 2010 to 2015, to quantify the impact of comorbidities on referral outcome, and to assist in identifying referrals unlikely to proceed to donation early in the post hospital referral process.

#### **MATERIALS AND METHODS**

We performed a cohort study of NSW OTDS referral logs from January 2010 to December 2015. Data obtained were used to create an Organ Donor Risk Profile Database of all referrals made for solid organ transplantation in this time. Referral logs before 2013 were predominantly paper based, where referrals from 2013 onwards were recorded electronically. Data extracted included date of referral, referring hospital, date of birth, gender and cause of death. To characterize the comorbidity burden of referrals, we collected medical history, including history diabetes, hypertension, hyperlipidemia, cardiac disease, vascular disease, cerebrovascular disease, respiratory disease, chronic liver disease (CLD), chronic kidney disease (CKD), and malignancy. Referral outcomes were nondonors (unsuitable for donation or family consent not obtained) and donors (comprising both actual donors who proceeded to retrieval of at least 1 organ, and intended donors where workup was initiated but abandoned before retrieval). When considering this impact of comorbidity burden on referral outcome, nondonors whose families declined to consent for donation were excluded from analyses to avoid confounding results.

To estimate disease burden among donor referrals, we considered age:  $\geq 65$  years old and the presence or absence of comorbidities including diabetes, hypertension, hyperlipidemia, cardiac disease, vascular disease, cerebrovascular disease, respiratory disease, CKD, CLD, and malignancy. Recognizing that chronic diseases may aggregate, these comorbidities were summed for each donor if present to estimate overall disease burden. KDRIs were calculated for referrals between January 2014 and December 2015 using the KDRI median and 2015 scaling factor of 1.2175 as this was the most recent available, and corresponded with included data. We were unable to calculate these indices for earlier referrals due to insufficient required data for nondonors before the introduction of electronic recording in 2013.

Statistical analyses were conducted in Stata 14.2. We described total referrals, donors and nondonors over time, to identify changes in referral patterns 2010-2015. Wilcoxontype nonparametric trend tests<sup>6</sup> were used to identify any significant change over time. Univariable and multivariable logistic regression models (odds ratio [OR], 95% confidence intervals [95% CI]) were used to estimate likelihood of not proceeding to donation given the presence or absence of comorbidities. The multivariable model initially included all variables, which were then removed sequentially in order of least significance, until all remaining variables were statistically significant (P < 0.01). The resulting model was then used to predict the probability of becoming an organ donor given the presence or absence of these comorbidities. Model performance was assessed using the area under the receiver-operating-characteristic curve<sup>7</sup> and the Hosmer-Lemeshow test for goodness of fit. Ethics approval was obtained through the University of Sydney Research Integrity and Ethics Administration.

## RESULTS

#### Epidemiology

We reviewed 2977 referrals (Figure 1). Of these, 669 (22%) were donors and 2308 (78%) did not progress to donation (nondonors). Figure 2 shows referral pattern 2010–2015, demonstrating the increase in donation through both donation after circulatory death and donation after brain death pathways, with the rise in the number of donors greatly exceeded by the increase in total number of referrals. Although nondonors were twice as likely to be  $\geq$ 65 years old than donors (Table 1), mean age of donors increased significantly between 2010 and 2015, from 47.0 to 52.2 years (*P* < 0.001), with the mean age of nondonors increasing from 58.9 to 62.0 across this period (*P* < 0.001). Although males were 20% more likely to be referred for organ donation than females (Table 1), once referred, females were slightly more likely to become donors, with 379 males (22% of males) and 286 females (24% of females) proceeding to donate organs.

Table 1 demonstrates that with the exception of cerebrovascular disease and hyperlipidemia, the prevalence of all comorbidities was greater among nondonors than donors. Donors were particularly much less likely to have a history of cardiac or CKD than nondonors. The prevalence of all comorbidities among the total population of referrals increased significantly

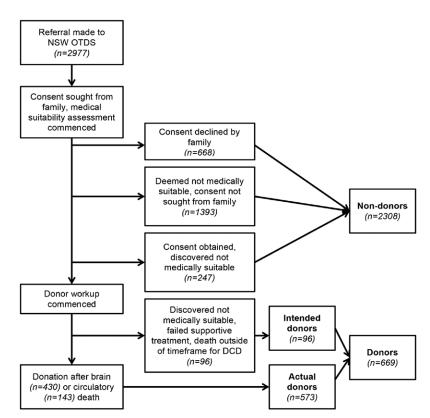


FIGURE 1. NSW organ donor referral process. DCD, donation after circulatory death; NSW, New South Wales; OTDS, Organ and Tissue Donation Service.

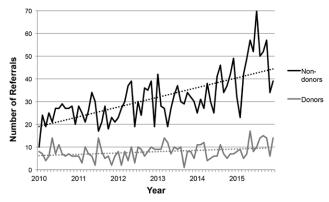


FIGURE 2. NSW organ donor referrals January 2010–December 2015. Dashed lines are linear trend lines. NSW, New South Wales.

between 2010 and 2015 (P < 0.001), with the exception of cerebrovascular disease, which significantly decreased in prevalence across this period (P = 0.005). From 2010 to 2015, mean number of comorbidities per referral, used to estimate total comorbidity burden, increased from 1.7 to 2.8 conditions for all referrals (P < 0.001), 1.4 to 2.2 for donors (P < 0.001), and 1.9 to 3.0 for nondonors (P < 0.001).

Nondonors were significantly more likely to have a history of malignancy than donors. Of the 37 donors who had a history of cancer, 14 (38%) had primary brain tumors, 5 (14%) had prostate cancer, 4 (11%) had previously excised noninvasive melanoma, 2 (5%) had thyroid cancer, 1 (3%) had cervical cancer, and 11 (29%) had other or unspecified cancers.

## **Comorbidity Burden Predicting Referral Outcome**

Consent was declined by the family of the referral in 668 (22%) of 2977 cases, leaving 2309 (78%) referrals in our

analysis (Figure 1). Our final multivariable model for predicting referral outcome included those variables significantly (P < 0.01) associated with not proceeding to donation, which were ≥65 years old, hyperlipidemia, cardiac disease, cerebrovascular disease, CKD, CLD, malignancy, and nonmetropolitan hospital location (Table 2). Of these, malignancy (OR 3.91, 95% CI 2.71-5.66, P < 0.001) and CKD (OR 3.45,95% CI 1.99-5.98, P < 0.001) were most strongly associated with not proceeding to donation. Conversely, the presence of hyperlipidemia (OR 0.38 95% CI 0.29-0.51, P < 0.001) and cerebrovascular disease (OR 0.69, 95% CI 0.57-0.85, P < 0.001) were associated with a referral progressing to organ donation. The area under the receiver-operating-characteristic curve of this model was 0.74, with the Hosmer-Lemeshow test not being significant (P = 0.40). After allowing for the combined effects of comorbidities, vascular disease, diabetes, hypertension, and respiratory disease were not significantly associated with referral outcome.

Table 3 outlines the predicted probabilities, derived from our final multivariable model, of proceeding to donation based on the presence or absence of combinations of key comorbidities significantly impacting referral outcome. The probability of proceeding to donation ranged from <1% (corresponding to those donors  $\geq$ 65 y of age and with CKD, CLD and malignancy or cerebrovascular disease) to 54% (corresponding to those donors <65 y of age and with cerebrovascular disease only).

#### DISCUSSION

In our cohort study, we described the distribution of comorbidities among 2977 people referred for organ donation in Australia from 2010 to 2015. Both organ donor referral and actual donation rates increased over this time. Our

# TABLE 1.

#### Characteristics of NSW organ donation referrals by outcome

		Nondonors; N (%)	Donors; N (%)	Total; N (%)	Trend over time; direction, P	
Total		2308 (78)	669 (22)	2977 (100)	-	
Demographics						
Sex	Male	1376 (60)	379 (57)	1755 (59)	-, 0.62	
	Female	907 (40)	286 (43)	1193 (41)	_	
Referring hospital	Regional	336 (15)	71 (11)	407 (14)	+, 0.84	
	Metropolitan	1972 (85)	598 (89)	2570 (86)	_	
Age, y	Mean (±SD)	58.3 (±19)	49.5 (±18)	56.3 (±19)	_	
	≥65	966 (42)	140 (21)	1106 (37)	+, <0.001	
	<65	1342 (58)	529 (79)	1871 (63)	_	
Comorbidities						
Diabetes		397 (17)	77 (12)	474 (16)	+, <0.001	
Hypertension		759 (33)	196 (29)	955 (32)	+, <0.001	
Hyperlipidemia		297 (13)	121 (18)	418 (14)	+, <0.001	
Cardiac disease		868 (38)	146 (22)	1014 (34)	+, <0.001	
Vascular disease		170 (7)	26 (4)	196 (7)	+, <0.001	
Cerebrovascular disease		958 (42)	299 (45)	1257 (42)	-, 0.005	
Respiratory disease		315 (14)	81 (12)	396 (13)	+, <0.001	
CKD		199 (9)	16 (2)	215 (7)	+, <0.001	
CLD		120 (5)	18 (3)	138 (5)	+, <0.001	
Malignancy		362 (16)	37 (6)	399 (10)	+, <0.001	
Summary measures of col	morbidities					
Mean number of como	rbidities (±SD)	2.3 (±1.8)	1.7 (±1.7)	2.1 (±1.8)	+, <0.001	
Mean KDRI (±SD)		2.7 (±1.8)	2.6 (±1.7)	2.6 (±1.7)	-, 0.472	

+, Positive trend, increasing 2010–2015; -, negative trend, decreasing 2010–2015; CLD, chronic liver disease; CKD, chronic kidney disease; KDRI, Kidney Donor Risk Index; NSW, New South Wales; SD, standard deviation.

#### TABLE 2.

## Univariable and multivariable analysis of the effect of comorbidity and demographics on likelihood of a referral not proceeding to donation

		Univariab	le	Multivariable		
		OR (95% CI)	Р	OR (95% CI)	Р	
Demographics						
Sex	Male	1.01 (0.99-1.02)	0.118	_	_	
	Female	_		_	_	
Referring hospital	Regional	1.62 (1.22-2.15)	0.001	1.56 (1.16-2.11)	0.003	
	Metropolitan	_	-	_	_	
Age, y	≥65	3.23 (2.62-3.98)	< 0.001	3.37 (2.67-4.27)	< 0.001	
0.17	<65	_	-	_	_	
Comorbidities						
Diabetes		1.78 (1.36-2.32)	< 0.001	_	_	
Hypertension		1.18 (0.97-1.44)	0.092	_	_	
Hyperlipidemia		0.65 (0.51-0.83)	< 0.001	0.38 (0.29-0.51)	< 0.001	
Cardiac disease		2.42 (1.97-2.98)	< 0.001	2.12 (1.68-2.68)	< 0.001	
Vascular disease		2.20 (1.43-3.38)	< 0.001	_	_	
Cerebrovascular disease		0.75 (0.62-0.90)	0.002	0.69 (0.57-0.85)	< 0.001	
Respiratory disease		1.26 (0.96-1.65)	0.091	_	_	
CKD		4.93 (2.93-8.30)	< 0.001	3.45 (1.99-5.98)	< 0.001	
CLD		2.55 (1.53-4.23)	< 0.001	3.00 (1.76-5.12)	< 0.001	
Malignancy		4.03 (2.83-5.73)	< 0.001	3.91 (2.71-5.66)	< 0.001	
Chronic liver disease		2.55 (1.53-4.23)	< 0.001	3.00 (1.76-5.12)	< 0.001	
Summary measures of comor	bidities					
Number of comorbidities (±		1.24 (1.17-1.31)	<0.001	_	-	

Cl, confidence intervals; CKD, chronic kidney disease; CLD, chronic liver disease; OR, odds ratio; SD, standard deviation.

data indicated that potential donors with a greater burden of disease are now more frequently being referred for consideration for organ donation, contributing to the growing proportion of referrals that do not proceed to donate. Our results indicated that average age of both organ donor referrals and actual donors increased significantly between 2010 and 2015. Although advanced donor age has been impact kidney graft function,<sup>8</sup> this may be acceptable

# TABLE 3.

#### Impact of comorbidities on predicted probability (%) of becoming an organ donor

			Malignancy +				Malignancy –			
			Age ≥65		Age <65		Age ≥65		Age <65	
			CLD +	CLD –	CLD +	CLD –	CLD +	CLD –	CLD +	CLD –
CKD +	Cardiac disease +	CVD -	<1	1	1	3	2	3	3	12
		CVD+	<1	2	2	4	2	7	7	15
	Cardiac disease -	CVD -	<1	2	2	5	3	5	6	18
		CVD+	<1	2	3	8	4	11	10	34
CKD —	Cardiac disease +	CVD -	2	3	3	9	5	12	10	29
		CVD+	2	6	4	15	5	18	18	40
	Cardiac disease -	CVD -	2	6	10	18	10	21	20	43
		CVD+	4	9	9	23	13	28	28	54

CKD, chronic kidney disease; CLD, chronic liver disease; CVD, cerebrovascular disease.

compared with alternatives including protracted dialysis for those on the kidney waiting list, with the risk of recipient deterioration or death during this time, particularly in older recipients.<sup>9,10</sup> However, donors  $\geq$ 65 years old are unlikely to donate, particularly if additional comorbidities such as CKD or cardiac disease are present.

The increasing prevalence of comorbidities among organ donor referrals over the 6 years in this study reflects the growing chronic disease burden in Australia at large. We found that the presence of comorbidities variably predicted likelihood of donation, with overall disease burden and particular comorbidity combinations being most important in determining referral outcome. Common comorbidities such as diabetes and hypertension were poor predictors of likelihood of donation. This study did not consider recipient factors in detail, because the decision about whether to proceed with an organ donor is made before the generation of any organ-recipient matching, and organ retrieval may be underway before recipients are finalized. However, other studies have shown that these donors may be particularly useful when matched appropriately to older or marginal recipients.<sup>11</sup> Our data indicate that at the organ-procurement service level, potential donors with combinations of comorbidities that confer a lower likelihood of donation, such as a history of cardiac disease, CKD, and malignancy, could be deprioritized compared with referrals without these comorbidities during times of pressure from multiple referrals, to facilitate optimal resource allocation to those referrals most likely to proceed to donate organs.

Our study defined a donor as a referral that proceeded to donate at least 1 organ. Given that kidney transplants account for half of all deceased organ transplants in Australia,<sup>12</sup> comorbidities that strongly impacts renal function may have played a particularly significant role in determining the likelihood of a referral proceeding to donate, partially explaining why the presence of CKD was so significant in our results. In the context of donation of specific organs, such as liver or cardiac transplantation, other comorbidities may be of greater importance.

While the presence of most comorbidities either reduced the likelihood of donation or did not significantly impact referral outcome, the presence of cerebrovascular was associated with a greater likelihood of donation. Cerebrovascular diseases account for only 6.8% of deaths in the broader Australian population,<sup>13</sup> but are the most common cause of among organ donors in Australia (48%)<sup>1</sup> and many other regions worldwide.<sup>14</sup> Similar findings have been reported in a recent study by Pilcher et al,<sup>15</sup> where a strong association between cerebrovascular disease and potential for donation was demonstrated.

Despite women being almost twice as likely to register as organ donors in Australia,<sup>16</sup> only 40% of organ donor referrals were females. This may partly be explained by women having a greater life expectancy than men and so dying older, and young men having a higher age-specific death rate than young women.<sup>17</sup> However, this runs counter to the higher rates of many comorbidities in males,<sup>18</sup> which this study determined significantly impact on likelihood of becoming an organ donor. As a result, this difference is not entirely explained. That regional hospital location was associated with non donation reflects one of the challenges to delivering health care in Australia, where potential donors may be geographically isolated.

Although malignancy is widely considered to be a contraindication to organ donation,<sup>19,20</sup> a small number of organ donors had a history of cancer. Of these, most had malignancies that carried a very low risk of transmission to the transplant recipient, notably primary brain cancer.<sup>21,22</sup> There may be overlooked opportunities for organ donation among the 16% of nondonors who had a history of cancer, in cases where the malignancy was of low risk and the potential donor otherwise medically suitable. Further study into the utilization of organs from donors with a history of malignancy with a low potential for transmission to the recipient is warranted.

This study drew upon an extensive database to answer a novel question regarding the organ donor referral process in Australia. However, our study was limited by the data collected on donor referrals. We were unable to measure disease severity, which may have influenced the statistical significance of common comorbidities such as hyperlipidemia and hypertension. Medical histories tended to be recorded in greater detail for donors than nondonors. This may have resulted in an underestimation of the comorbidity burden among nondonors, or an overestimation of the significance of comparably minor comorbidities. We hypothesized that this may have led to the association between the presence of hyperlipidemia and increased likelihood organ donation, as hyperlipidemia was recorded less frequently among nondonors than would be expected.<sup>18</sup> Given that the Transplantation Society of Australia and New Zealand guidelines do not consider hyperlipidemia in the context of organ donation and transplantation, this may not need to be collected by the OTDS in the future.<sup>20</sup> Other limitations included an inability to access other data including medications and test results of potential donors, and the exclusion of tissue-only referrals and donors. Whether our work is generalizable to other settings may depend on whether the organ procurement systems are comparable.

Our study demonstrated that organ donors and donor referrals in Australia are increasingly older, with a greater burden of comorbidities. Moving towards routine referrals of all potential organ donors may help to ensure that no potential opportunity for organ donation is overlooked, but will likely increase the pressure on organ procurement services to evaluate high volumes of referrals. Our results also demonstrated that donor comorbidities play a significant and quantifiable role in determining the likelihood of a referral proceeding to donate, and represent a potential opportunity to optimize the efficiency of the organ donor referral process in Australia when needed while still encouraging increasing numbers of referrals from hospitals. Using information readily obtainable from donor medical histories, it is possible to identify many of the potential organ donors referred that have a low probability of being medically suitable for donation. These referrals should not be excluded or disregarded particularly in the context of encouraging routine referral of potential organ donors, but the predicted probabilities derived from our model could be applied at the organ-procurement services level to facilitate efficient resource allocation among multiple donor referrals when prioritization is required. Importantly, this may streamline the donor referral process without reducing the absolute number of referrals made from hospitals, to avoid adversely impacting the recent valuable gains that have been made in organ donation rates. This would allow for the sustainable provision of quality services in the donor referral process, to facilitate organ donor referral and donation rates continuing to increase in the future.

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