Published in final edited form as:

Pediatr Crit Care Med. 2015 July ; 16(6): 576–582. doi:10.1097/PCC.0000000000000414.

Impact of Kidney Disease on Survival in Neonatal Extracorporeal Life Support

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Abstract

Objective—To investigate the prevalence and survival to discharge of neonates with kidney disease who received extracorporeal life support.

Design—We analyzed the Extracorporeal Life Support Organization international registry of neonates (< 30 d old) who received extracorporeal life support from 1989 to 2012. We used *International Classification of Diseases and Related Health Problems*, 9th Revision, Clinical Modification, codes to identify neonates with kidney disease at time of cannulation for extracorporeal life support.

Setting—Participating Extracorporeal Life Support Organization centers.

Patients—All neonates who received extracorporeal life support at an Extracorporeal Life Support Organization center from 1989 to 2012.

Interventions—We performed bivariate logistic regression to estimate associations between survival and covariates. We used unadjusted and adjusted logistic regression to compare survival to discharge between neonates with and without kidney disease. Odds ratios were estimated separately for three groups based on extracorporeal life support indication: pulmonary indication without congenital diaphragmatic hernia, pulmonary indication with congenital diaphragmatic

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Dr. Brogan has disclosed that he does not have any potential conflicts of interest.

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hernia, and cardiac indication. Adjusted models included covariates identified as significant in bivariate models for each group.

Measurements and Main Results—The primary outcome measure was survival to discharge from hospitalization. Of the 28,755 neonates who received extracorporeal life support, 405 had kidney disease (extracorporeal life support indication: 210 pulmonary indication without congenital diaphragmatic hernia, 65 pulmonary indication with congenital diaphragmatic hernia, and 130 cardiac indication). Survival was lower in neonates with kidney disease than those without (49% vs 82% pulmonary indication without congenital diaphragmatic hernia, 25% vs 51% pulmonary indication with congenital diaphragmatic hernia, 21% vs 41% cardiac indication). Kidney disease was associated with reduced survival in adjusted models (95% CI for odds ratio 0.31–0.59 pulmonary indication without congenital diaphragmatic hernia, 0.27–0.89 pulmonary indication with congenital diaphragmatic hernia, 0.31–0.77 cardiac indication).

Conclusions—Neonates with kidney disease who receive extracorporeal life support have poorer survival to discharge compared with other neonates who receive extracorporeal life support, suggesting that kidney disease should be considered when making extracorporeal life support initiation decisions.

Keywords

bioethics; decision making; dialysis; extracorporeal life support; kidney; renal

In the setting of refractory respiratory failure or cardiac failure, extracorporeal life support (ECLS) may be considered a temporary lifesaving support measure (1). Consideration of ECLS candidacy requires the patient to have a “reversible condition with a high predicted mortality rate”; however, universal acceptance of any specific inclusion or exclusion criterion for ECLS does not exist and exact criteria are center specific (1, 2).

The reported prevalence of acute kidney injury (AKI) and of renal replacement therapy (RRT) in neonates and children on ECLS is high (25% and 46%, respectively) (3). AKI and receipt of RRT have both been shown to be independent predictors for mortality in neonates receiving ECLS (2–9).

Little is known about the outcomes of neonates with antenatal kidney abnormalities or known postnatal kidney disease who receive ECLS. Irreversible organ damage such as severe or end-stage kidney disease may be considered by some a relative contraindication for ECLS unless the patient is a candidate for organ transplant. The application of this relative contraindication to individual center protocols is unknown. It is unclear whether neonates with kidney disease were included in the early randomized controlled trials of ECLS in neonates with a pulmonary indication for support (10–12) or whether this population was excluded due to a “condition incompatible with normal quality of life” (10) or a “reason to question continuation of conventional therapy” (12). Limited data indicate that some neonates with kidney disease who have received ECLS for respiratory failure have acceptable outcomes with survival to discharge reported as high as 80% (13, 14). These positive outcomes may not reflect current practices at many centers, which now include the consideration and treatment of more complex neonates with multiple organ failure (15, 16).

The goal of this study was to investigate the survival to discharge of neonates (< 30 d) with diagnosis of kidney disease and compare these outcomes and complications with neonates without kidney disease. We hypothesized that neonates with kidney disease would have poorer survival to discharge compared with other neonates who receive ECLS support.

METHODS

We analyzed data from the Extracorporeal Life Support Organization (ELSO) international registry, which contains all patients who receive ECLS at 170 participating centers (<http://www.else.org>, accessed October 29, 2013). This accounts for a majority of patients who receive ECLS in North America and an increasing percentage of centers worldwide. The retrospective cohort included neonates (< 30 d old) who received ECLS from 1989 to 2012. Analysis was restricted to the first ECLS run for each patient. To account for outcome differences between primary organ failure indication for ECLS support, we stratified neonates into three groups by ECLS indication (pulmonary indication without congenital diaphragmatic hernia [pulmonary/no CDH], pulmonary indication with congenital diaphragmatic hernia [PCDH], cardiac indication). Neonates with extracorporeal cardiopulmonary resuscitation indication for ECLS were excluded due to the emergent nature of resuscitation, which likely would not afford time to consider preexisting kidney disease.

Neonates with any *International Classification of Diseases and Related Health Problems*, 9th Revision, Clinical Modification (ICD-9), code consistent with kidney disease or structural genitourinary anomaly entered at time of initiation were classified as having kidney disease. Creatinine was not used in our definition of kidney disease due to the coding in the ELSO dataset, which assessed for creatinine level more than 1.5 mg/dL. Neonates with acute renal failure (ICD-9 584) alone were not considered to have kidney disease. We also did not consider AKI in our definition of kidney disease, as there is no associated ICD-9 code for the diagnosis. Neonates with no diagnosis information ($n = 104$) were excluded from analysis. We further categorized neonates with kidney disease as having congenital anomalies of kidney and urinary tract (CAKUT), polycystic kidney disease (PKD), congenital nephrotic syndrome (CNS), chronic kidney disease (CKD), vesicoureteral reflux (VUR), or unspecified kidney disease. If neonates had ICD-9 codes belonging to more than one category, they were assigned to the most specific classification (order of increasing specificity: unspecified → CKD → CAKUT → VUR → PKD → CNS). For the purposes of this study, we classified neonates as receiving RRT if they underwent dialysis, hemofiltration, or continuous arteriovenous hemodialysis. We defined AKI according to the ELSO definition as serum creatinine level more than 1.5 mg/dL at any point during monitoring. This definition has been applied to this population previously (3).

This study was approved by the Institutional Review Board of Seattle Children's Hospital.

Statistical Methods

The primary outcome measure was survival to discharge from hospitalization. Descriptive statistics were prepared for the entire cohort and by presence/absence of kidney disease within each of the three indication groups. We evaluated the following covariates for

association with survival to discharge, using bivariate logistic regression models: sex, race (non-White vs White), gestational age in weeks, age in days at ECLS onset, weight in kg at ECLS onset, era in which ECLS occurred (1989–2000 vs 2001–2012), ECLS mode (venoarterial vs venovenous), creatinine (≥ 1.5 mg/dL vs < 1.5 mg/dL), and RRT (yes/no). We used unadjusted and adjusted logistic regression to estimate associations between survival to discharge and presence of any kidney disease. In an exploratory subanalysis, we categorized all kidney disease as CAKUT or other and estimated associations with survival for each category. Adjusted multivariable models included covariates found to be significant at the 0.1 level in bivariate model results. Bivariate and multivariable regression modeling were conducted separately for each indication group. All testing was two-sided and conducted at the 0.05 level of significance. All statistical analyses were performed using Stata version 12 (StataCorp, College Station, TX).

RESULTS

Of the 28,755 neonates who received ECLS between 1989 and 2012 and met inclusion criteria, 405 (1.4%) had kidney disease (ECLS indication: 210 pulmonary/no CDH, 65 PCDH, and 130 cardiac). Patient characteristics are summarized in Table 1. RRT was used in a higher proportion of neonates with kidney disease than those without (44% vs 17% pulmonary/no CDH, 51% vs 27% PCDH, and 53% vs 37% cardiac). Survival to discharge was lower in neonates with kidney disease than those without (49% vs 82% pulmonary/no CDH, 25% vs 51% PCDH, and 21% vs 41% cardiac) and in those neonates with kidney disease who received RRT than those without kidney disease who received RRT (33% vs 63% pulmonary/no CDH, 24% vs 35% PCDH, and 16% vs 26% cardiac).

Bivariate associations of demographic and clinical covariates with survival to discharge for each ECLS indication are summarized in Table 2. Among neonates with a pulmonary/no CDH indication, the only covariate evaluated that was not significant was male sex. Male sex and ECLS mode were found to be nonsignificant among neonates with a PCDH indication, while ECLS mode (only one patient received venovenous ECLS) and age at ECLS onset were found to be nonsignificant among neonates with a cardiac indication.

In both unadjusted and adjusted logistic regression models, kidney disease was associated with reduced survival to discharge for each indication (Table 3). The magnitude of association was similar across all indications (adjusted 95% CI for odds ratio 0.31–0.59 pulmonary/no CDH, 0.27–0.89 PCDH, and 0.31–0.77 cardiac). All covariates included in the multivariable models were significant except for non-White race among neonates with PCDH indication and male sex among neonates with cardiac indication.

In a subgroup analysis, survival to discharge among ECLS recipients was greater for those with CAKUT ICD-9 diagnosis than for those with other kidney diseases for each indication (66% vs 28% pulmonary/no CDH, 50% vs 12% PCDH, and 38% vs 13% cardiac). In adjusted regression models, kidney disease diagnoses other than CAKUT were associated with reduced survival across all indications (adjusted 95% CI for odds ratio 0.12–0.34 pulmonary/no CDH, 0.08–0.54 PCDH, and 0.12–0.48 cardiac) while CAKUT was not

(adjusted 95% CI for odds ratio 0.49–1.16 pulmonary/no CDH, 0.54–3.18 PCDH, and 0.63–2.45 cardiac).

DISCUSSION

Neonates with kidney disease who receive ECLS have lower likelihood of surviving to discharge than other neonates who receive ECLS. This association is seen in each ECLS indication and remained significant in a multivariable model including patient and ECLS variables associated with severity of illness and development of AKI or RRT requirement.

Overall survival to discharge among neonates receiving RRT in our cohort appears similar to those reported by other groups using data from single centers (5, 8, 17). Similar to other reports, we observed an association with poorer overall survival among pulmonary CDH and non-CDH groups in the more recent era of ECLS, likely reflecting an evolving patient selection criterion among centers, resulting in consideration and treatment of increasingly complex patients. This has been previously demonstrated in the pediatric population of ECLS recipients (16, 18). The opposite association was found among the cardiac indication group.

The lack of an association between CAKUT and survival to discharge in multivariate analysis was a surprising finding. We are unaware of previous studies that have found this relationship. CAKUT comprise a broad spectrum of renal and urinary tract malformations, which include renal agenesis, renal hypo/dysplasia, multicystic kidney dysplasia, duplex renal collecting system, ureteropelvic junction obstruction, megaureter, posterior urethral valves, and VUR (19). It has been documented that CAKUT is a common etiology of end-stage kidney disease requiring initiation of RRT in the neonatal period (20). It is possible that our study was underpowered to describe the relationship or that the anomalies that led centers to code CAKUT were relatively benign, while those diagnoses considered more severe were coded more specifically (e.g., PKD, VUR), although this is speculation. The patient with CAKUT had lower rates of serum creatinine more than 1.5 mg/dL and initiation of RRT compared with the remaining kidney patients for each indication.

The purpose of this study was to help inform the clinicians and families of neonates with kidney disease in decision making at the time of ECLS initiation. For that reason, we did not include AKI, which is both associated with ECLS therapy and an independent predictor of mortality among neonates who receive ECLS therapy (3, 5). Coding in the ELSO dataset was not sensitive enough to detect most episodes of AKI by newer accepted criteria, such as pediatric modified Renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function, and End-stage renal disease (21), Acute Kidney Injury Network (22), or Kidney Disease: Improving Global Outcomes (23, 24), and there is no ICD-9 coding for AKI. The smallest cutoff of serum creatinine in the ELSO dataset (> 1.5 mg/dL) is significantly higher than published reference values for serum creatinine in term neonates, which range from 0.42 to 0.92 mg/dL (2.5–97.5%) at day of birth to 0.26 to 0.58 mg/dL at 1 week old (25).

It is possible that undetected AKI could confound the association between kidney disease at cannulation and survival to discharge. We do not feel this is likely. Acute renal failure (ICD-9 584) was coded in 16 neonates (4.0%) classified as kidney disease and 955 neonates (4.5%) without kidney disease. Furthermore, the association of survival to discharge with kidney disease remained significant after adjustment for both RRT requirement and serum creatinine more than 1.5 mg/dL, the marker in the ELSO dataset for AKI.

Our study has a number of important limitations. The most significant is our definition of kidney disease. Identification of patients was limited to ICD-9 code alone. Coding was further limited as 159 patients were classified as kidney disease “unspecified” (Appendix 1). This limitation prevented us from analyzing the association of specific kidney disease and survival in this population. Given the young age of our cohort, it is possible that some with kidney disease were not detected and thus not classified by ICD-9 coding. Underreporting of renal dysfunction and acute renal failure in preterm neonates has been demonstrated by an analysis of 66,000 neonates in the Pediatrix Medical Group dataset (26). A similar phenomenon could have occurred at ELSO centers.

Outcomes from the ECLS registry do not include long-term patient survival, long-term kidney survival, transplantation, or neurodevelopmental outcomes. Data from single centers suggest the majority of neonates who require RRT while on ECLS will recover renal function; however, the likelihood of renal recovery may be much lower in this population with kidney disease noted prior to ECLS initiation (17, 27).

The evolution of ECLS has provided neonates a chance for survival in situations previously considered uniformly fatal. As ECLS and non-ECLS care advances, patient eligibility criteria for ECLS should evolve in order to provide support in the hope of improving long-term outcomes. Our findings indicate that neonates with kidney disease have lower survival to discharge after receipt of ECLS than those without and suggest that consideration of kidney disease is relevant when making treatment decisions and obtaining parental permission for therapy. This study also suggests the need for future research to assess for specific associations between kidney disease and long-term survival to identify future interventions to improve long-term outcomes of this critically ill population.

Acknowledgments

Supported, in part, by the Seattle Children’s Hospital Research Institute Center for Clinical and Translational Research.

Dr. Wightman received support for article research from the National Institutes of Health (NIH). His institution received grant support from the NIH training grant (training grant for Wightman nephrology fellowship 5 T32 DK007662). Ms. Bradford’s institution received grant support from National Center for Advancing Translational Sciences of the NIH (grant UL1TR000423). Dr. Symons received grant support from the Seattle Children’s Center for Clinical and Translational Research Faculty Research Support Fund (internal grant to pay for statistical support/analysis on this project), received royalties from UpToDate, and received support for travel from the University of Missouri (Annual Dialysis Conference, speaker) and the University of California San Diego (Continuous Real Replacement Therapy Conference, speaker).

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APPENDIX 1. Diagnosis Codes

Kidney Disease Diagnosis	Code	Frequency
Congenital anomalies of kidney and urinary tract	585	3
	585.9	1
	586	3
	589	1
	589.9	1
	591	39
	593	1
	593.5	2
	593.81	4
	593.89	1
	599.6	4
	753	24
	753.1	6
	753.15	13
	753.2	22
	753.21	1
	753.22	5
	753.29	39
	753.3	15
	753.5	1
	753.6	10
	753.7	1

Kidney Disease Diagnosis	Code	Frequency
	753.9	4
Polycystic kidney disease	753.12	11
	753.14	6
	753.15	1
	753.19	6
Congenital nephrotic syndrome	581.9	4
Chronic kidney disease	585	47
	585.6	3
	585.9	3
	753.1	1
Vesicoureteral reflux	585	1
	593.7	5
Unspecified	586	126
	588	1
	593.89	1
	593.9	31

Table 1

Extracorporeal Life Support Recipient Characteristics

Variable	Pulmonary Indication Without CDH (<i>n</i> = 17,623)		Pulmonary Indication With CDH (<i>n</i> = 6,132)		Cardiac Indication (<i>n</i> = 5,000)	
	No Kidney Disease (<i>n</i> = 17,413)	Kidney Disease (<i>n</i> = 210)	No Kidney Disease (<i>n</i> = 6,067)	Kidney Disease (<i>n</i> = 65)	No Kidney Disease (<i>n</i> = 4,870)	Kidney Disease (<i>n</i> = 130)
Weight at cannulation, kg, mean (sd)	3.4 (0.6)	3.2 (0.7)	3.1 (0.5)	3 (0.6)	3.2 (0.6)	3.1 (0.6)
Gestational age, wk, median (IQR)	40 (38–40)	38 (36–39)	38 (37–40)	38 (37–39)	38 (37–39)	38 (37–39)
Age at ECMO onset in days, median (IQR)	1 (1–3)	2 (1–3)	1 (0–2)	1 (0–3)	7 (3–12)	6 (3–11)
Kidney diagnosis, <i>n</i> (%)						
Congenital anomalies of kidney and urinary tract		117 (56)		22 (34)		42 (32)
Polycystic kidney disease		19 (9)		2 (3)		2 (2)
Congenital nephrotic syndrome		2 (1)		1 (2)		1 (1)
Chronic kidney disease		17 (8)		11 (17)		16 (12)
Vesicoureteral reflux		4 (2)		0 (0)		0 (0)
Unspecified		51 (24)		29 (45)		69 (53)
Sex, <i>n</i> (%)						
Female	7,264 (42)	63 (30)	2,576 (42)	30 (46)	1,965 (40)	47 (36)
Male	10,049 (58)	147 (70)	3,460 (57)	35 (54)	2,863 (59)	82 (63)
Missing	100 (1)	0 (0)	31 (1)	0 (0)	42 (1)	1 (1)
Race, <i>n</i> (%)						
Asian	677 (4)	5 (2)	199 (3)	3 (5)	201 (4)	3 (2)
Black	3,913 (22)	48 (23)	771 (13)	8 (12)	507 (10)	23 (18)
Hispanic	2,119 (12)	35 (17)	875 (14)	13 (20)	565 (12)	16 (12)
Other	744 (4)	17 (8)	224 (4)	2 (3)	225 (5)	5 (4)
White	8,994 (52)	103 (49)	3,803 (63)	39 (60)	2,451 (50)	82 (63)
Missing	966 (6)	2 (1)	195 (3)	0 (0)	921 (19)	1 (1)
ECMO era, <i>n</i> (%)						
2001–2012	6,641 (38)	169 (80)	2,840 (47)	55 (85)	3,498 (72)	111 (85)

Variable	Pulmonary Indication Without CDH (<i>n</i> = 17,623)		Pulmonary Indication With CDH (<i>n</i> = 6,132)		Cardiac Indication (<i>n</i> = 5,000)	
	No Kidney Disease (<i>n</i> = 17,413)	Kidney Disease (<i>n</i> = 210)	No Kidney Disease (<i>n</i> = 6,067)	Kidney Disease (<i>n</i> = 65)	No Kidney Disease (<i>n</i> = 4,870)	Kidney Disease (<i>n</i> = 130)
1989–2000	10,772 (62)	41 (20)	3,227 (53)	10 (15)	1,372 (28)	19 (15)
Initial ECMO mode, <i>n</i> (%)						
Venovenous	6,128 (35)	63 (30)	1,057 (17)	16 (25)	107 (2)	1 (1)
Venoarterial	11,223 (64)	146 (70)	4,997 (82)	49 (75)	4,716 (97)	129 (99)
Missing	62 (0)	1 (0)	13 (0)	0 (0)	47 (1)	0 (0)
Acute kidney injury (creatinine 1.5), <i>n</i> (%)	1,320 (8)	65 (31)	509 (8)	11 (17)	676 (14)	35 (27)
RRT, <i>n</i> (%)	2,977 (17)	93 (44)	1,629 (27)	33 (51)	1,816 (37)	69 (53)
Survived if required RRT, <i>n</i> (%)	1,878 (63)	31 (33)	563 (35)	8 (24)	477 (26)	11 (16)
Acute renal failure (ICD-9 584), <i>n</i> (%)	309 (2)	11 (5)	226 (4)	2 (3)	420 (9)	3 (2)
Survived to discharge, <i>n</i> (%)	14,342 (82)	103 (49)	3,074 (51)	16 (25)	1,990 (41)	27 (21)

CDH = congenital diaphragmatic hernia, IQR = interquartile range, RRT = renal replacement therapy, ICD = *International Classification of Diseases and Related Health Problems*, 9th Revision, Clinical Modification.

Covariate Associations With Survival to Discharge in Bivariate Logistic Regression Models, Including Patients With and Without Preexisting Kidney Disease

Table 2

Variable	Pulmonary Without CDH			Pulmonary With CDH			Cardiac		
	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Male sex	1.05	0.97–1.13	0.23 ^a	1.03	0.93–1.15	0.51 ^a	1.12	0.99–1.25	0.06
Non-White race	1.33	1.23–1.45	< 0.01	0.88	0.79–0.98	0.02	0.76	0.67–0.87	< 0.01
Gestational age, wk	1.24	1.22–1.27	< 0.01	1.16	1.13–1.20	< 0.01	1.13	1.09–1.18	< 0.01
Age at ECLS onset, d	0.90	0.90–0.91	< 0.01	1.04	1.03–1.06	< 0.01	1.00	0.99–1.01	0.48 ^a
Weight at ECLS onset kg	1.87	1.74–2.01	< 0.01	2.05	1.85–2.27	< 0.01	1.74	1.58–1.93	< 0.01
ECLS era ^b	1.52	1.41–1.64	< 0.01	1.37	1.24–1.52	< 0.01	0.82	0.73–0.94	< 0.01
Venoarterial mode ^c	0.58	0.53–0.64	< 0.01	0.90	0.79–1.03	0.12	0.81	0.55–1.19	0.29
Creatinine 1.5	0.24	0.22–0.27	< 0.01	0.35	0.29–0.43	< 0.01	0.40	0.33–0.48	< 0.01
Renal replacement therapy	0.26	0.24–0.29	< 0.01	0.41	0.36–0.46	< 0.01	0.36	0.32–0.41	< 0.01

CDH = congenital diaphragmatic hernia, OR = odds ratio, ECLS = extracorporeal life support.

^aOmitted from multivariable analysis.

^b1989–2000 (reference, 2001–2012).

^cReference: venovenous ECLS mode

Table 3
Association of Kidney Disease With Survival to Discharge in Unadjusted and Adjusted Logistic Regression Models

Variable	Pulmonary Without CDH			Pulmonary With CDH			Cardiac		
	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Unadjusted model									
Kidney disease	0.21	0.16–0.27	0.00	0.32	0.18–0.56	0.00	0.38	0.25–0.58	0.00
Multivariable (adjusted) model									
Male sex	—	—	—	—	—	—	1.07	0.92–1.25	0.37
Non-White race	1.22	1.11–1.34	<0.01	0.92	0.82–1.03	0.16	0.76	0.65–0.89	<0.01
Gestational age, wk	1.12	1.10–1.15	<0.01	1.07	1.03–1.11	<0.01	1.05	1.00–1.10	0.04
Age at ECLS onset, d	0.92	0.91–0.93	<0.01	1.05	1.03–1.07	<0.01	—	—	—
Weight at ECLS onset, kg	1.52	1.40–1.66	<0.01	1.82	1.61–2.06	<0.01	1.63	1.41–1.89	<0.01
ECLS era ^a	1.56	1.41–1.72	<0.01	1.32	1.18–1.48	<0.01	0.68	0.54–0.86	<0.01
Venoarterial mode ^b	0.63	0.57–0.70	<0.01	—	—	—	—	—	—
Creatinine 1.5	0.28	0.24–0.33	<0.01	0.42	0.33–0.54	<0.01	0.58	0.46–0.74	<0.01
Dialysis	0.43	0.39–0.48	<0.01	0.44	0.39–0.51	<0.01	0.45	0.38–0.53	<0.01
Kidney disease	0.43	0.31–0.59	<0.01	0.49	0.27–0.89	0.02	0.48	0.31–0.77	<0.01

CDH = congenital diaphragmatic hernia, OR = odds ratio, ECLS = extracorporeal life support.

^a1989–2000 (reference, 2001–2012).

^bReference venovenous ECLS mode.

Dashes indicate the variable was not included in model.