

Supplementary Data

Association Between Dexmedetomidine Use and Mortality in Patients With COVID-19 Receiving Invasive Mechanical Ventilation: A US National COVID Cohort Collaborative (N3C) Study

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Table S1. Median Time Between First COVID-19 Indication and Hospitalization Following Propensity Score Matching			
	DEX	No DEX	<i>P</i>
Model 1 days from positive test to hospitalization (SD)	1.11 (2.8)	1.16 (2.7)	0.58
Model 2 days from positive test to hospitalization (SD)	1.32 (2.9)	0.84 (2.0)	0.02
Abbreviations: SD = standard deviation			

Table S2. Pre Propensity Score Matching Variables at Hospital Admission

	Model 1^a			Model 2^b		
	N = 6,109			N = 955		
Variable	No DEX (n = 3,107)	DEX (n = 3,002)	SMD	No DEX (n = 340)	DEX (n = 615)	SMD
Age (SD)	63.4 (14.1)	59.1 (15.0)	0.30	63.2 (14.0)	58.6 (14.6)	0.32
Male Sex (%)	1999 (64.3)	1893 (63.1)	0.03	221 (65.0)	383 (62.3)	0.06
Race (%)						
Black	450 (14.5)	476 (15.9)	0.08	< 20*	22 (3.6)	0.18
Other	182 (5.9)	129 (4.3)		< 20*	50 (8.1)	
Unknown	717 (23.1)	727 (24.2)		52 (15.3)	90 (14.6)	
White	1758 (56.6)	1670 (55.6)		261 (76.8)	453 (73.7)	
Ethnicity (%)						
Hispanic	552 (17.8)	679 (22.6)	0.13	45-65 (13-19)*	79 (12.8)	0.13
Not Hispanic	2325 (74.8)	2150 (71.6)		277 (81.5)	514 (83.6)	
Unknown	230 (7.4)	173 (5.8)		< 20*	22 (3.6)	
Active Cancer (%)	248 (8.6)	207 (6.9)	0.04	28 (8.2)	31 (5.0)	0.13
Cardiovascular Disease (%)						
Hypertension	2247 (72.3)	1971 (65.7)	0.14	228 (67.1)	351 (57.1)	0.21
Coronary Artery Disease	702 (22.6)	543 (18.1)	0.11	78 (22.9)	99 (16.1)	0.17
Congestive Heart Failure	678 (21.8)	661 (22.0)	< 0.01	83 (24.4)	113 (18.4)	0.15
Chronic respiratory disease (%)						
Asthma	350 (11.3)	336 (11.2)	< 0.01	34 (10.0)	60 (9.8)	0.01
COPD	803 (27.9)	798 (28.4)	0.01	103 (30.3)	162 (26.3)	0.09
Interstitial Lung Disease	72 (2.4)	68 (2.4)	0.01	< 20*	24 (3.9)	0.01
Apnea	489 (15.7)	510 (17.0)	0.03	57 (16.8)	115 (18.7)	0.05
Immunosuppression (%)						
HIV	29 (0.9)	33 (1.1)	0.02	< 20*	< 20	0.03
Kidney Disease (%)						
Chronic	811 (26.1)	640 (21.3)	0.11	71 (20.9)	96 (15.6)	0.14
End-Stage	144 (4.6)	124 (4.1)	0.02	< 20*	< 20*	0.03
Liver Disease (%)						
Cirrhosis	85 (2.7)	95 (3.2)	0.03	< 20*	< 20*	0.03
Hepatitis B	< 20*	< 20*	0.01	< 20*	< 20*	0.08
Hepatitis C	48 (1.5)	93 (3.1)	0.10	< 20*	< 20*	0.08
Metabolic Disease						
Obesity (%)	1198 (38.6)	1197 (39.9)	0.03	136 (40.0)	237 (38.5)	0.03
Morbid Obesity (%)	495 (15.9)	544 (18.1)	0.06	55 (16.2)	122 (19.8)	0.10
BMI (SD)	32.3 (9.1)	33.2 (9.3)	0.10	32.7 (9.4)	33.7 (9.2)	0.10
Diabetes (%)	1374 (44.2)	1301 (43.3)	0.02	137 (40.3)	226 (36.7)	0.07
mCCI (SD)	2.5 (2.4)	2.3 (2.3)	0.08	2.2 (2.3)	1.8 (2.0)	0.19

Abbreviations: BMI = body mass index; COPD = chronic obstructive pulmonary disease; DEX = dexmedetomidine; HIV = human immunodeficiency virus; mCCI = modified Charlson Comorbidity Index; SD = standard deviation; SMD = standardized mean difference

^a Model 1: Health system sites included that lacked PaO₂/FiO₂ data

^b Model 2: Only health system sites that had PaO₂/FiO₂ data were included

* Values less than 20 denoted as < 20 per N3C policy. Ranges used for complementary values to prevent < 20 calculation.

Table S3. Pre Propensity Score Matching ICU Variables

	Model 1^a			Model 2^b		
	N = 6,109			N = 955		
Variable	No DEX (n = 3,107)	DEX (n = 3,002)	SMD	No DEX (n = 340)	DEX (n = 615)	SMD
PaO2/FiO2 (SD)	--	--		89.1 (69.6)	83.1 (41.3)	0.10
mSOFA score (SD) ^c	4.8 (2.3)	4.7 (2.2)	0.05	8.7 (2.0)	8.6 (1.7)	0.10
Sedative Use (%)						
GABA receptor ligand (%)	3091 (99.5)	2950 (98.3)	0.12	331 (97.4)	592 (96.3)	0.06
Propofol	2576 (82.9)	2670 (88.9)	0.17	256 (75.3)	487 (79.2)	0.09
Midazolam	2432 (78.3)	2558 (85.2)	0.18	259 (76.2)	515 (83.7)	0.19
Lorazepam	1656 (53.3)	1582 (52.7)	0.01	185 (54.4)	364 (59.2)	0.10
Ketamine	509 (16.4)	742 (24.7)	0.21	61 (17.9)	239 (38.9)	0.48
Opioid use (%)	2876 (92.6)	2917 (97.2)	0.21	322 (94.7)	591 (96.1)	0.07
Corticosteroid (any) use (%)	2464 (79.3)	2497 (83.2)	0.10	268 (78.8)	491 (79.8)	0.03
Methylprednisolone	714 (23.0)	595 (19.8)	0.08	68 (20.0)	97 (15.8)	0.11
Dexamethasone	1683 (54.2)	1921 (64.0)	0.20	198 (58.2)	408 (66.3)	0.17
Hydrocortisone	632 (20.3)	706 (23.5)	0.08	75 (22.7)	162 (26.6)	0.09
Prednisone	234 (7.5)	288 (9.6)	0.07	36 (10.6)	93 (15.1)	0.14
Remdesivir use (%)	696 (22.4)	870 (29.0)	0.15	84 (24.7)	193 (31.4)	0.15
Antibiotic (any) use (%)	2451 (78.9)	2805 (93.4)	0.43	259 (76.2)	542 (88.1)	0.32
Anticoagulant (any) use (%)	2987 (96.1)	2928 (97.5)	0.08	309 (90.9)	584 (95.0)	0.16
Heparin	2343 (75.4)	2230 (74.3)	0.03	215 (63.2)	426 (69.3)	0.13
LMWH	2115 (68.1)	2179 (72.6)	0.10	200 (58.8)	373 (60.7)	0.04
Factor Xa inhibitor	487 (15.7)	536 (17.9)	0.06	49 (14.4)	105 (17.1)	0.07
Direct thrombin inhibitor	54 (1.7)	204 (6.8)	0.25	< 20*	68 (11.1)	0.37
Warfarin	71 (2.3)	107 (3.6)	0.08	< 20*	36 (5.9)	0.08
Inhaled NO Use (%)	< 20*	< 20*	0.01	< 20*	< 20*	0.03
Vasopressor Use (%)	2677 (86.2)	2655 (88.4)	0.07	286 (84.1)	553 (89.9)	0.17
Paralytic / NMB (%)	2644 (85.1)	2672 (89.0)	0.12	236 (69.4)	508 (82.6)	0.31
RRT (%)	282 (9.1)	295 (9.8)	0.03	29 (8.5)	98 (15.9)	0.23
ECMO (%)	114 (3.7)	203 (6.8)	0.14	< 20*	50 (8.1)	0.38

Abbreviations: DEX = dexmedetomidine; ECMO = extracorporeal membrane oxygenation; GABA = gamma-aminobutyric acid; LMWH = low molecular weight heparin; mSOFA= modified Sequential Organ Failure Assessment; NMB = neuromuscular blockade; NO = nitric oxide; PaO2/FiO2 = partial pressure of arterial oxygen to the fraction of inspired oxygen; RRT = renal replacement therapy; SD = standard deviation; SMD = standardized mean difference

^a Model 1: Health system sites included that lacked PaO2/FiO2 data

^b Model 2: Only health system sites that had PaO2/FiO2 data were included

^c mSOFA score in Model 1 has central nervous system and respiratory component removed; mSOFA score in Model 2 has central nervous system component removed

* Values of less than 20 denoted as < 20 as specified by N3C Data Enclave policy

Table S7. Vaccinated Prior to a COVID-19 Diagnosis (Post-Propensity Score Matching)

	Model 1^a			Model 2^b		
	N = 3,806			N = 576		
Variable	No DEX (n = 1,903)	DEX (n = 1,903)	SMD	No DEX (n = 288)	DEX (n = 288)	SMD
Vaccinated (%)	73 (3.8)	65 (3.4)	0.02	< 20*	< 20*	0.16

Abbreviations: DEX = dexmedetomidine; SMD = standardized mean difference

^a Model 1: Health system sites included that lacked PaO₂/FiO₂ data^b Model 2: Only health system sites that had PaO₂/FiO₂ data were included

* Values of less than 20 denoted as < 20 as specified by N3C Data Enclave policy

Table S8. Interleukin-6 (IL-6) Inhibitor Use (Tocilizumab and Sarilumab) (Post-Propensity Score Matching)

	Model 1^a			Model 2^b		
	N = 3,806			N = 576		
Variable	No DEX (n = 1,903)	DEX (n = 1,903)	SMD	No DEX (n = 288)	DEX (n = 288)	SMD
IL-6 inhibitor (%)	106 (5.6)	104 (5.5)	< 0.01	< 20*	< 20*	0.19

Abbreviations: DEX = dexmedetomidine; SMD = standardized mean difference

^a Model 1: Health system sites included that lacked PaO₂/FiO₂ data^b Model 2: Only health system sites that had PaO₂/FiO₂ data were included

* Values of less than 20 denoted as < 20 as specified by N3C Data Enclave policy

Table S9. Janus Kinase (JAK) Inhibitor Use (Baricitinib and Tofacitinib) (Post-Propensity Score Matching)

	Model 1^a			Model 2^b		
	N = 3,806			N = 576		
Variable	No DEX (n = 1,903)	DEX (n = 1,903)	SMD	No DEX (n = 288)	DEX (n = 288)	SMD
JAK inhibitor (%)	< 20*	< 20*	< 0.001	< 20*	< 20*	< 0.001

Abbreviations: DEX = dexmedetomidine; SMD = standardized mean difference

^a Model 1: Health system sites included that lacked PaO₂/FiO₂ data^b Model 2: Only health system sites that had PaO₂/FiO₂ data were included

* Values of less than 20 denoted as < 20 as specified by N3C Data Enclave policy

	DEX use (any time) (n = 3,806)		DEX use (<=3.5 days) (n = 2,857)		DEX use (>3.5 days) (n = 2,852)	
	aHR (95%CI)	P	aHR (95%CI)	P	aHR (95%CI)	P
DEX exposure	0.81 (0.73, 0.9)	< 0.01	0.67 (0.6, 0.76)	< 0.01	0.71 (0.61, 0.83)	< 0.01
mCCI	1.03 (1.01, 1.05)	< 0.01	1.03 (1, 1.05)	0.03	1.04 (1.01, 1.06)	< 0.01
BMI	1 (1, 1.01)	0.10	1.01 (1, 1.02)	< 0.01	1 (1, 1.01)	0.38
Age at COVID hospitalization	1.04 (1.04, 1.04)	< 0.01	1.04 (1.03, 1.04)	< 0.01	1.04 (1.03, 1.04)	< 0.01
mSOFA ^a	1.15 (1.12, 1.18)	< 0.01	1.15 (1.12, 1.19)	< 0.01	1.15 (1.12, 1.19)	< 0.01
Dexamethasone exposure	1.08 (0.97, 1.21)	0.17	1.05 (0.93, 1.18)	0.47	1.01 (0.88, 1.14)	0.94
Remdesivir exposure	0.9 (0.81, 1.01)	0.08	0.91 (0.81, 1.03)	0.14	0.88 (0.77, 0.99)	0.04
Data partner 1	1.54 (1.24, 1.92)	< 0.01	1.58 (1.26, 2)	< 0.01	1.41 (1.04, 1.92)	0.03
Data partner 2	0.68 (0.59, 0.78)	< 0.01	0.72 (0.61, 0.85)	< 0.01	0.66 (0.56, 0.77)	< 0.01
Data partner 3	0.68 (0.56, 0.83)	< 0.01	0.65 (0.52, 0.82)	< 0.01	0.74 (0.59, 0.93)	0.01
Data partner 4	1.09 (0.92, 1.29)	0.34	1.22 (1.01, 1.46)	0.04	1.02 (0.83, 1.25)	0.85
Data partner 5	0.66 (0.56, 0.79)	< 0.01	0.83 (0.69, 1)	0.05	0.68 (0.56, 0.82)	< 0.01
Data partner other	0.41 (0.34, 0.5)	< 0.01	0.43 (0.36, 0.53)	< 0.01	0.38 (0.31, 0.47)	< 0.01

Abbreviations: BMI = body mass index; DEX = dexmedetomidine; mCCI = modified Charlson Comorbidity Index; mSOFA = modified Sequential Organ Failure Assessment

^a mSOFA score modified with central nervous system and respiratory component removed

Table S11: Model 2: Multivariable Cox Regression with Dexmedetomidine as a Time-Varying Covariate (Full Study: January 1, 2020 to November 3, 2022), Propensity Score Matched Cohort

	DEX use (any time) (n = 576)		DEX use (<=4 days) (n = 448)		DEX use (>4 days) (n = 416)	
	aHR (95%CI)	P	aHR (95%CI)	P	aHR (95%CI)	P
DEX exposure	0.95 (0.72, 1.25)	0.73	0.72 (0.53, 0.98)	0.04	0.97 (0.65, 1.45)	0.87
mCCI	1.09 (1.02, 1.16)	0.01	1.08 (1.01, 1.16)	0.03	1.11 (1.04, 1.19)	< 0.01
BMI	0.99 (0.98, 1.01)	0.21	1 (0.98, 1.01)	0.83	1 (0.98, 1.01)	0.58
Age at COVID hospitalization	1.03 (1.02, 1.05)	< 0.01	1.04 (1.02, 1.05)	< 0.01	1.04 (1.02, 1.05)	< 0.01
PaO2/FiO2	0.99 (0.99, 1)	0.01	0.99 (0.99, 1)	0.01	0.99 (0.99, 1)	0.04
mSOFA ^a	1.16 (1.08, 1.24)	< 0.01	1.17 (1.09, 1.26)	< 0.01	1.16 (1.07, 1.26)	< 0.01
Dexamethasone exposure	1.09 (0.84, 1.41)	0.50	1.05 (0.79, 1.38)	0.75	1.11 (0.81, 1.53)	0.50
Remdesivir exposure	0.88 (0.64, 1.21)	0.43	0.77 (0.55, 1.09)	0.14	0.85 (0.59, 1.24)	0.40
Data partner 3	0.71 (0.53, 0.96)	0.03	0.57 (0.4, 0.81)	< 0.01	0.79 (0.57, 1.11)	0.17
data partner 6	0.47 (0.33, 0.65)	< 0.01	0.4 (0.28, 0.59)	< 0.01	0.4 (0.27, 0.61)	< 0.01
data partner other	0.18 (0.02, 1.49)	0.11	0.55 (0.07, 4.3)	0.57	0.17 (0.02, 1.51)	0.11

Abbreviations: BMI = body mass index; DEX = dexmedetomidine; mCCI = modified Charlson Comorbidity Index; mSOFA = modified Sequential Organ Failure Assessment; PaO₂/FiO₂ = partial pressure of arterial oxygen to the fraction of inspired oxygen

^a mSOFA score modified with central nervous system component removed

Table S13: Model 1: Multivariable Cox Regression With Dexmedetomidine as a Time-Varying Covariate (Pre-Dexamethasone Era, January 1, 2020 to July 30, 2020), Propensity Score Matched Cohort

	DEX use (any time) (n = 909)	
	aHR (95%CI)	P
DEX exposure	0.54 (0.42, 0.69)	< 0.01
mCCI	1.08 (1.03, 1.14)	< 0.01
BMI	1 (0.99, 1.02)	0.76
Age at COVID hospitalization	1.05 (1.04, 1.06)	< 0.01
mSOFA ^a	1.21 (1.14, 1.28)	< 0.01
Dexamethasone exposure	0.88 (0.65, 1.19)	0.41
Remdesivir exposure	0.97 (0.63, 1.48)	0.89
Data partner 1	1.72 (0.77, 3.85)	0.19
Data partner 2	0.93 (0.62, 1.4)	0.73
Data partner 3	1.18 (0.7, 1.99)	0.54
Data partner 4	1.15 (0.72, 1.82)	0.57
Data partner 5	1 (0.68, 1.47)	1.00
Data partner other	0.65 (0.42, 1.01)	0.06
Abbreviations: BMI = body mass index; DEX = dexmedetomidine; mCCI = modified Charlson Comorbidity Index; mSOFA = modified Sequential Organ Failure Assessment		
^a mSOFA score modified with central nervous system and respiratory component removed		

Table S14: Model 1: Multivariable Cox Regression With Dexmedetomidine as a Time-Varying Covariate (Current Dexamethasone Era, July 30, 2020 to November 3, 2022), Propensity Score Matched Cohort

	DEX use (any time) (n = 2,897)	
	aHR (95%CI)	P
DEX exposure	0.89 (0.79, 1)	0.06
mCCI	1.01 (0.99, 1.04)	0.25
BMI	1.01 (1, 1.01)	0.06
Age at COVID hospitalization	1.04 (1.03, 1.04)	< 0.01
mSOFA ^a	1.13 (1.09, 1.16)	< 0.01
Dexamethasone exposure	0.88 (0.76, 1.01)	0.08
Remdesivir exposure	0.86 (0.76, 0.96)	0.01
Data partner 1	1.38 (1.09, 1.73)	0.01
Data partner 2	0.64 (0.55, 0.75)	< 0.01
Data partner 3	0.58 (0.47, 0.72)	< 0.01
Data partner 4	1.11 (0.93, 1.34)	0.24
Data partner 5	0.61 (0.49, 0.76)	< 0.01
Data partner other	0.37 (0.3, 0.46)	< 0.01
Abbreviations: BMI = body mass index; DEX = dexmedetomidine; mCCI = modified Charlson Comorbidity Index; mSOFA = modified Sequential Organ Failure Assessment		
^a mSOFA score modified with central nervous system and respiratory component removed		

Table S15: Model 2: Multivariable Cox regression with Dexmedetomidine as a Time-Varying Covariate (Pre-Dexamethasone Era, January 1, 2020 to July 30, 2020), Propensity Score Matched Cohort

	DEX use (any time) (<i>n</i> = 73)	
	aHR (95%CI)	<i>P</i>
DEX exposure	0.22 (0.06, 0.78)	0.02
mCCI	1.19 (0.89, 1.59)	0.25
BMI	0.97 (0.89, 1.06)	0.53
Age at COVID hospitalization	1.08 (1.03, 1.13)	< 0.01
PaO2/FiO2	1 (0.99, 1.01)	0.86
mSOFA ^a	1.2 (0.89, 1.62)	0.24
Dexamethasone exposure	1.4 (0.44, 4.48)	0.57
Remdesivir exposure	1.84 (0.74, 4.58)	0.19
Data partner 3	0.49 (0.21, 1.16)	0.11
data partner 6	0.43 (0.16, 1.17)	0.10
data partner other	0 (0, 0)	< 0.01
Abbreviations: BMI = body mass index; DEX = dexmedetomidine; mCCI = modified Charlson Comorbidity Index; mSOFA = modified Sequential Organ Failure Assessment; PaO2/FiO2= partial pressure of arterial oxygen to the fraction of inspired oxygen		
^a mSOFA score modified with central nervous system component removed		

Table S16: Model 2: Multivariable Cox Regression With Dexmedetomidine as a Time-Varying Covariate (Current Dexamethasone Era, July 30, 2020 to November 3, 2022), Propensity Score Matched Cohort

	DEX use (any time) (<i>n</i> = 503)	
	aHR (95%CI)	<i>P</i>
DEX exposure	1.03 (0.77, 1.38)	0.83
mCCI	1.07 (1, 1.15)	0.06
BMI	0.99 (0.98, 1.01)	0.30
Age at COVID hospitalization	1.03 (1.02, 1.05)	< 0.01
PaO2/FiO2	0.99 (0.99, 1)	0.02
mSOFA ^a	1.16 (1.08, 1.24)	< 0.01
Dexamethasone exposure	0.99 (0.74, 1.31)	0.94
Remdesivir exposure	0.87 (0.62, 1.22)	0.42
Data partner 3	0.73 (0.52, 1.02)	0.07
data partner 6	0.5 (0.35, 0.71)	< 0.01
data partner other	0.28 (0.03, 2.6)	0.26
Abbreviations: BMI = body mass index; DEX = dexmedetomidine; mCCI = modified Charlson Comorbidity Index; mSOFA = modified Sequential Organ Failure Assessment; PaO2/FiO2= partial pressure of arterial oxygen to the fraction of inspired oxygen		
^a mSOFA score modified with central nervous system component removed		

Table S17: Number and Percent Death in Model 1 and Model 2 in Subgroup Analysis of Pre-Dexamethasone Era and Current Dexamethasone Era

	DEX group			No DEX group			
Model and subgroup	Patients (n)	Deaths (n)	Deaths (%)	Patients (n)	Deaths (n)	Deaths (%)	P
Model 1; Pre-Dexamethasone Era ^a	483	175	36.23	426	267	62.68	<0.01
Model 1; Current Dexamethasone Era ^b	1420	727	51.20	1477	1008	68.25	<0.01
Model 2: Pre-Dexamethasone Era ^a	31	< 20	masked	42	25	59.52	0.13
Model 2: Current Dexamethasone Era ^b	257	131	50.97	246	151	61.38	0.02

^a Pre-Dexamethasone Era were patients assessed between 1/1/20 – 7/30/2020

^b Current Dexamethasone Era were patients assessed between 7/30/2020 – 10/3/2022

Figure S1: Survival curve - Model 1: Multivariable Cox Regression With Dexmedetomidine as a Time-Varying Covariate (Full Study: January 1, 2020 to November 3, 2022), Propensity Score Matched Cohort

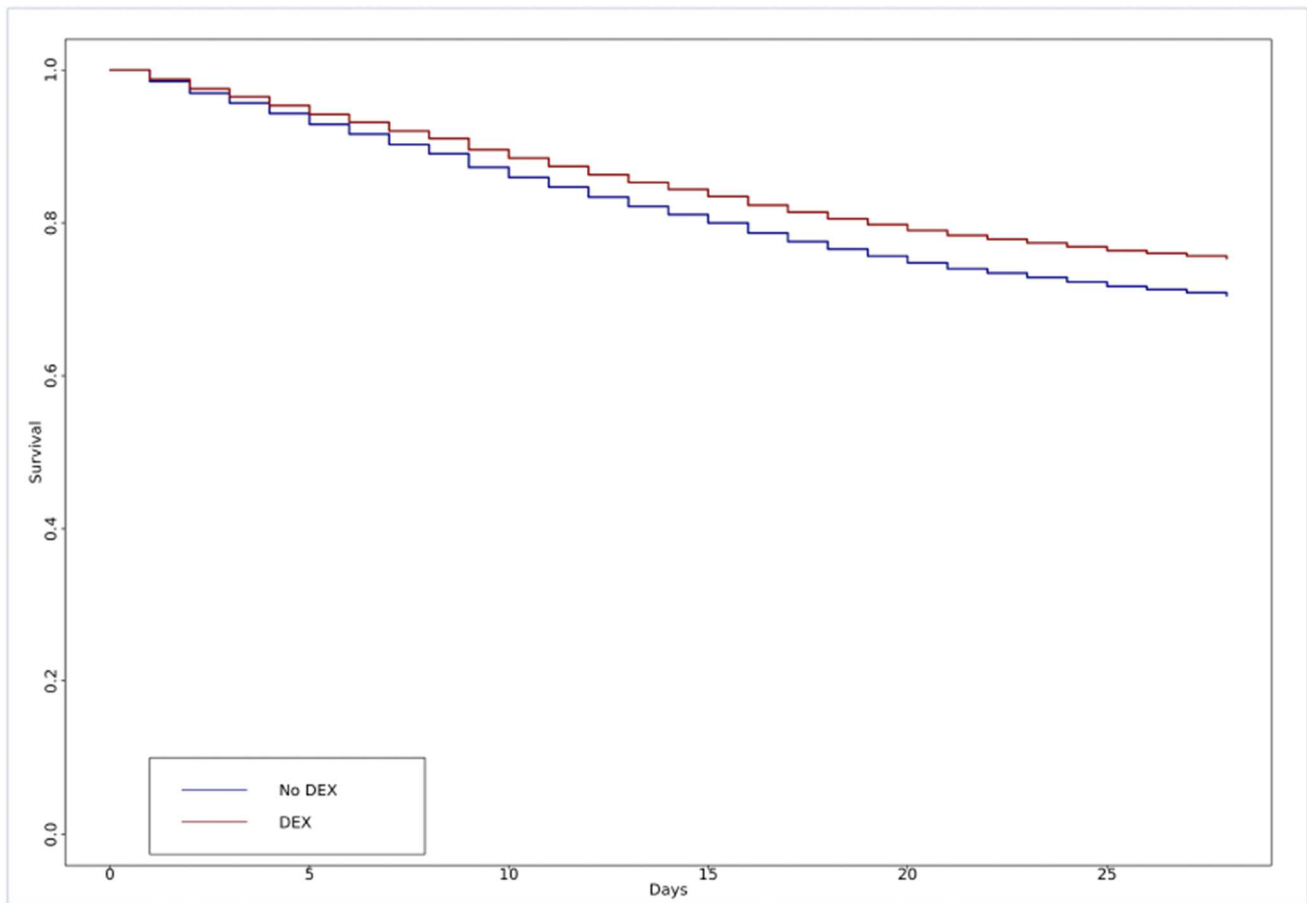


Figure S2: Survival curve - Model 2: Multivariable Cox Regression With Dexmedetomidine as a Time-Varying Covariate (Full Study: January 1, 2020 to November 3, 2022), Propensity Score Matched Cohort

