

Supplemental tables

Table S1. Descriptive statistics of discovery and 2 external validation cohorts including the proportion of missingness

	Discovery cohort Total (N=1804)	Missing ^a (%)	First validation cohort Total (N=288)	Missing ^b (%)	Second validation cohort Total (N=1401)	Missing ^c (%)
Male, n (%)	1061 (58.8)	0.0	160 (55.6)	0.0	788 (56.2)	0.0
Caucasian, n (%)	1641 (92.9)	2.1	263 (91.6)	0.3	1286 (93.5)	1.9
Age, y	57.2 (11.7)	0.0	56.1 (14.0)	0.0	57.8 (11.6)	0.0
BMI, kg/m ²	26.0 (4.5)	1.2	26.9 (4.6)	0.0	25.8 (4.2)	1.1
Current smoking, n (%)	99 (5.5)	0.1	29 (10.1)	0.7	80 (5.7)	0.1
Current alcohol consumption, n (%)	809 (45.0)	0.3	117 (40.9)	0.7	622 (44.5)	0.3
Comorbidities, n (%)		0.0		0.0		0.0
Diabetes mellitus	369 (20.5)		61 (21.2)		276 (19.7)	
Chronic lung disease	118 (6.5)		15 (5.2)		90 (6.4)	
Heart failure	104 (5.8)		13 (4.5)		72 (5.1)	
Hypertension	1531 (84.9)		233 (80.9)		1185 (84.6)	
Primary renal diagnosis, n (%)		32.7		10.1		34.4
Congenital/familial/hereditary renal disease	44 (3.6)		76 (29.3)		39 (4.2)	
Diabetic kidney disease	88 (7.2)		10 (3.9)		68 (7.4)	
Glomerulonephritis	309 (25.5)		57 (22.0)		220 (23.9)	
Vascular disease	111 (9.1)		29 (11.2)		81 (8.8)	
Interstitial nephritis/pyelonephritis/drug induced nephropathy/urolithiasis	108 (8.9)		14 (5.4)		78 (8.5)	
Secondary glomerular/other multisystemic disease	74 (6.1)		14 (5.4)		61 (6.6)	
Other	391 (32.2)		41 (15.8)		309 (33.6)	
Unknown	89 (7.3)		18 (6.9)		63 (6.9)	
eGFR, mL/min/1.73m ²	51.5 (18.8)	20.8	49.5 (18.6)	0.3	51.0 (18.9)	21.5
Transplant characteristics		20.8		0.0		21.5
First kidney transplant, n (%)	1226 (85.8)		227 (78.8)		941 (85.5)	
Time after transplantation, y	7.6 [4.0, 13.6]		6.9 [2.6, 13.3]		8.2 [4.3, 13.7]	
Last transplant						
Living, n (%)	936 (65.5)		200 (69.4)		695 (63.2)	
Immunosuppressive treatment, n (%)		21.6		0.0		22.5
Steroids	1074 (75.9)		219 (76.0)		841 (77.4)	
Azathioprine	147 (10.4)		34 (11.8)		102 (9.4)	
MMF/MPA	923 (65.2)		197 (68.4)		700 (64.5)	
Calcineurin inhibitor	1166 (82.4)		236 (81.9)		899 (82.8)	
mTOR inhibitor	104 (7.3)		17 (5.9)		96 (8.8)	
Nonseroconversion, n (%) ^d	836 (46.3)	0.0	124 (43.1)	0.0	358 (25.6)	0.0

^aMissing data in discovery cohort: Ethnicity (N=38); BMI (N=22); Smoking behavior (N=1); Use of alcohol (N=5); eGFR (N=375), Number of transplants (N=375); Time after transplantation (N=376); Living transplant (N=375); Use of steroids (N=389); Use of azathioprine (N=389); Use of MMF/MPA (N=389); Use of calcineurin inhibitor (N=389); Use of mTOR inhibitor (N=389); Primary renal diagnosis (N=590).

^bMissing data in first validation cohort: Ethnicity (N=1); Smoking behavior (N=2); Use of alcohol (N=2); eGFR (N=1), Primary renal diagnosis (N=29).

^cMissing data in second validation cohort: Ethnicity (N=27); BMI (N=15); Smoking behavior (N=1); Use of alcohol (N=4); eGFR (N=301), Number of transplants (N=301); Time after transplantation (N=301); Living transplant (N=301); Use of steroids (N=315); Use of azathioprine (N=315); Use of MMF/MPA (N=315); Use of calcineurin inhibitor (N=315); Use of mTOR inhibitor (N=315); Primary renal diagnosis (N=481).

^dNonseroconversion was defined with a level of SARS-CoV-2 spike S1-specific IgG antibodies of <50 BAU/mL (anti-SARS-CoV-2 RBD IgG ELISA assay) after the second vaccination in the discovery cohort or third vaccination in the second validation cohort and <10 BAU/mL (fluorescent bead-based multiplex immunoassay) after the second vaccination in the first validation cohort.

Abbreviations are: BMI, body mass index; eGFR, estimated glomerular filtration rate; MMF/MPA, mycophenolate mofetil/mycophenolic acid; mTOR, mammalian target of rapamycin

Table S2. Descriptive statistics of inclusion and exclusion cohort

	Inclusion cohort Total (N= 1804)	Exclusion cohort Total (N=1726)	p-value
Male, n (%)	1061 (58.8)	1028 (59.6)	0.677
Caucasian, n (%)	1641 (92.9)	1262 (88.8)	<0.001
Age, y	57.2 (11.7)	57.1 (15.3)	0.831
BMI, kg/m²	26.0 (4.5)	26.2 (4.6)	0.202
Current smoking, n (%)	99 (5.5)	98 (6.8)	0.153
Current alcohol consumption, n (%)	809 (45.0)	589 (40.6)	0.013
Comorbidities, n (%)			
Diabetes mellitus	369 (20.5)	392 (26.9)	<0.001
Chronic lung disease	118 (6.5)	105 (7.2)	0.494
Heart failure	104 (5.8)	99 (6.8)	0.253
Hypertension	1531 (84.9)	1209 (83.0)	0.170
Primary renal diagnosis, n (%)			0.555
Congenital/familial/hereditary renal disease	44 (3.6)	56 (4.8)	
Diabetic kidney disease	88 (7.2)	100 (8.6)	
Glomerulonephritis	309 (25.5)	273 (23.5)	
Vascular disease	111 (9.1)	105 (9.0)	
Interstitial nephritis/pyelonephritis/drug induced nephropathy/urolithiasis	108 (8.9)	98 (8.4)	
Secondary glomerular/other multisystemic disease	74 (6.1)	70 (6.0)	
Other	391 (32.2)	388 (33.4)	
Unknown	89 (7.3)	72 (6.2)	
eGFR, mL/min/1.73m²	51.5 (18.8)	50.7 (19.1)	0.281
Transplant characteristics			
First kidney transplant, n (%)	1226 (85.8)	1150 (85.6)	0.906
Time after transplantation, y	7.6 [4.0, 13.6]	7.6 [3.7, 13.3]	0.376
Last transplant			
Living, n (%)	936 (65.5)	833 (62.0)	0.059
Immunosuppressive treatment, n (%)			
Steroids	1074 (75.9)	1007 (75.4)	0.782
Azathioprine	147 (10.4)	119 (8.9)	0.211
MMF/MPA	923 (65.2)	878 (65.7)	0.819
Calcineurin inhibitor	1166 (82.4)	1128 (84.4)	0.168
mTOR inhibitor	104 (7.3)	93 (7.0)	0.748
Nonseroconversion, n (%)^a	836 (46.3)	906 (52.5)	<0.001

^aNonseroconversion was defined with a level of SARS-CoV-2 spike S1-specific IgG antibodies of <50 BAU/mL (anti-SARS-CoV-2 RBD IgG ELISA assay) after the second vaccination.

Abbreviations are: BMI, body mass index; eGFR, estimated glomerular filtration rate; MMF/MPA, mycophenolate mofetil/mycophenolic acid; mTOR, mammalian target of rapamycin

Table S3. Univariable and multivariable analysis of discovery cohort

Predictors	Discovery cohort Univariable OR [95% CI]	p-value	Discovery cohort Multivariable OR [95% CI]	p-value
MMF/MPA	5.41 [4.34, 6.78]	<0.001	5.45 [4.25, 7.03]	<0.001
Chronic lung disease	2.20 [1.50, 3.28]	<0.001	1.91 [1.23, 2.99]	0.004
Heart failure	1.56 [1.05, 2.33]	0.030	1.83 [1.14, 2.95]	0.013
Diabetes mellitus	1.88 [1.49, 2.38]	<0.001	1.65 [1.26, 2.15]	<0.001
Age, y	1.02 [1.01, 1.03]	<0.001	1.02 [1.02, 1.03]	<0.001
Time after transplantation, y	0.95 [0.94, 0.96]	<0.001	0.95 [0.93, 0.96]	<0.001
BMI, kg/m² per 5	0.94 [0.85, 1.04]	0.251	0.86 [0.73, 0.95]	0.004
eGFR, ml/min/1.73m² per 10	0.92 [0.88, 0.97]	0.002	0.82 [0.82, 0.90]	<0.001
Current alcohol use	0.73 [0.61, 0.88]	0.001	0.76 [0.61, 0.94]	0.012
First kidney transplant	0.93 [0.72, 1.21]	0.592	0.65 [0.47, 0.88]	0.006
mTOR inhibitor	0.38 [0.26, 0.56]	<0.001	0.59 [0.37, 0.93]	0.025
Calcineurin inhibitor	1.05 [0.83, 1.34]	0.672	0.52 [0.38, 0.72]	<0.001

Abbreviations are: MMF/MPA, mycophenolate mofetil/mycophenolic acid; eGFR, estimated glomerular filtration rate; BMI, body mass index; mTOR, mammalian target of rapamycin; CI, confidence interval

Supplemental figures

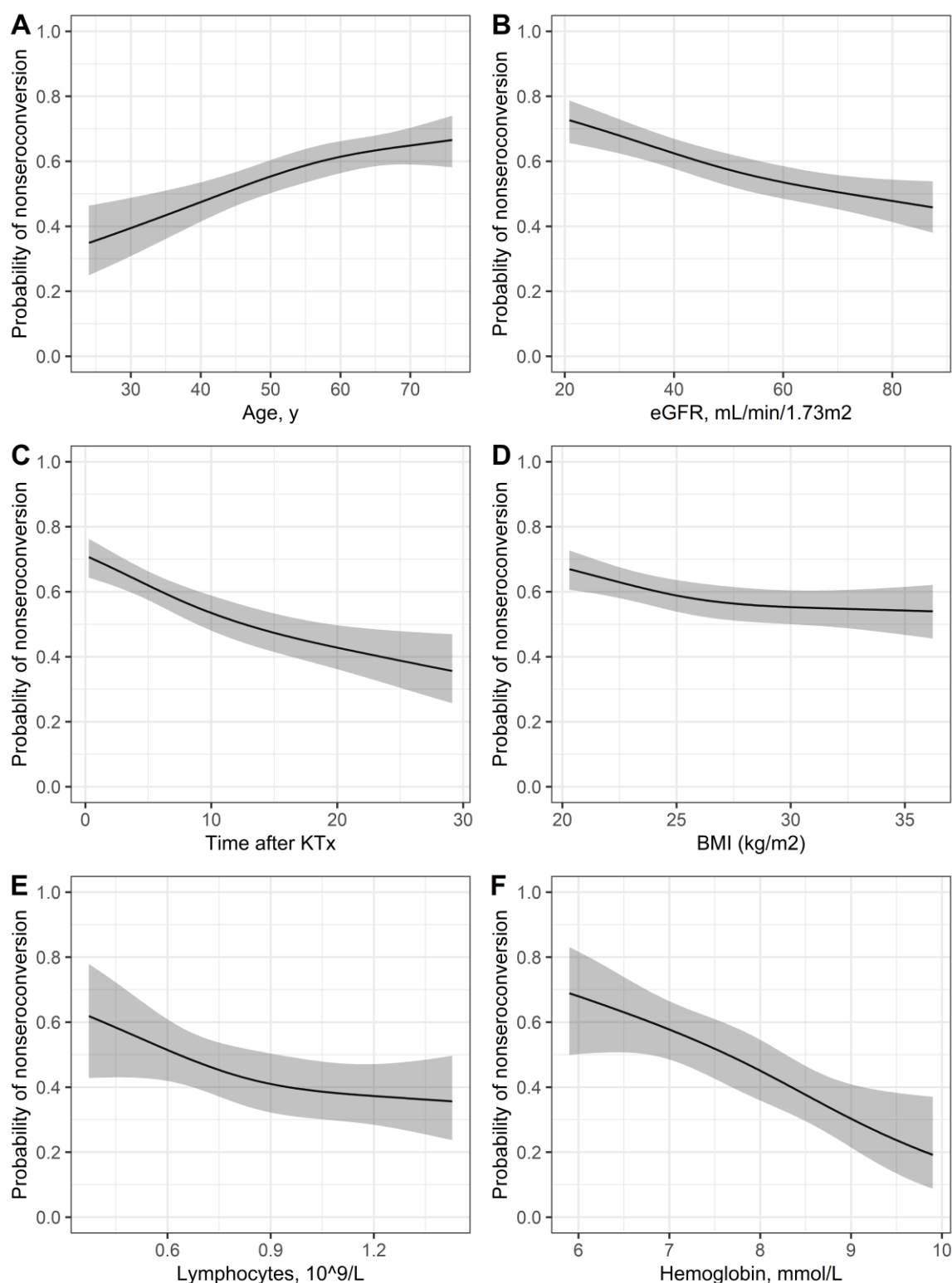


Figure S1. The continuous, linear predictors plotted against the probability of nonseroconversion to SARS-CoV-2 vaccination in KTR. (A-D) In all 4 models we used 3-knot restricted cubic spline analysis, corresponding to an age of 59 years, BMI of 25 kg/m², no alcohol use, no diabetes mellitus, chronic lung disease or heart failure, first KTx, 8 years after KTx, eGFR of 51 mL/min/1.73m², MMF/MPA use, calcineurin inhibitor use and no mTOR inhibitor use. (E-F) In this model we used 3-knot restricted cubic spline analysis, corresponding to a probability of nonseroconversion of 0.54.

Abbreviations are: SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus-2; KTR, kidney transplant recipients; MMF/MPA, mycophenolate mofetil/mycophenolic acid; mTOR, mammalian target of rapamycin; eGFR, estimated glomerular filtration rate; KTx, kidney transplantation; BMI, body mass index

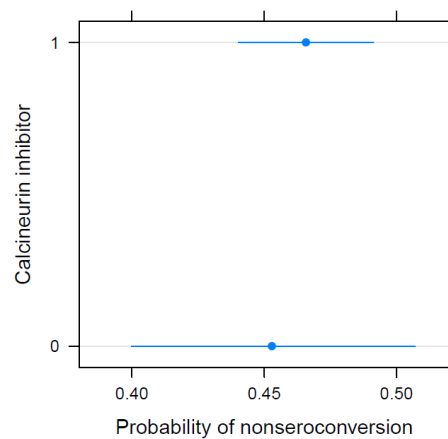
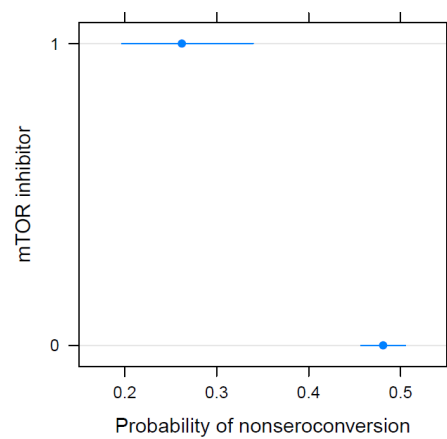
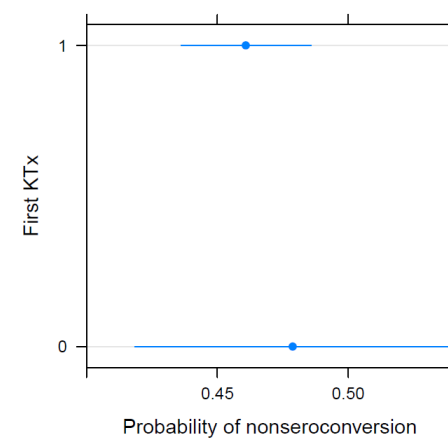
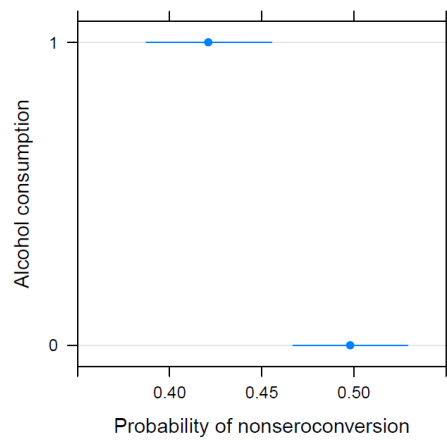
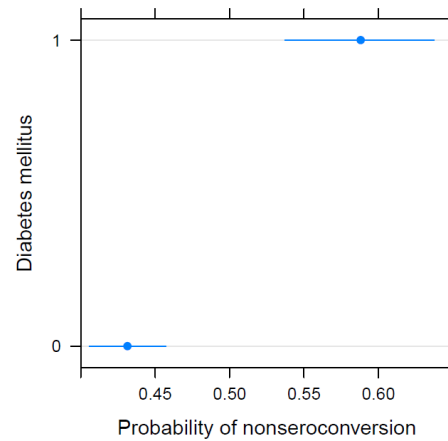
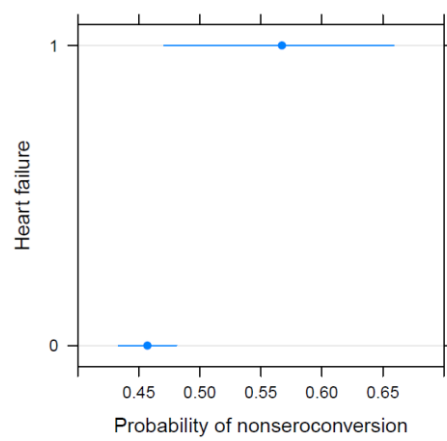
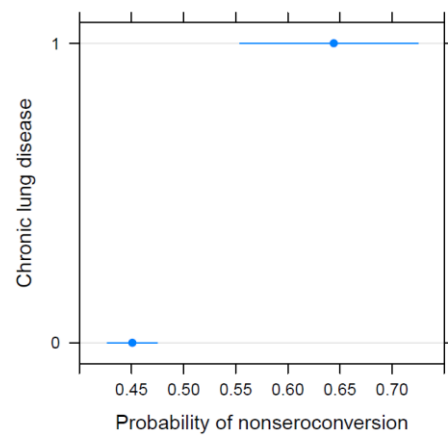
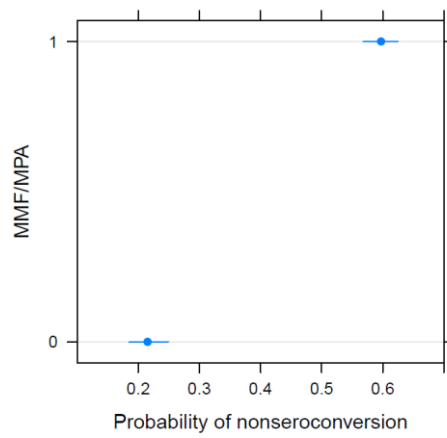


Figure S2. The binary, linear predictors plotted against the probability of nonseroconversion to SARS-CoV-2 vaccination in KTR.

Abbreviations are; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus-2; KTR, kidney transplant recipients; MMF/MPA, mycophenolate mofetil/mycophenolic acid; KTx, kidney transplantation; mTOR, mammalian target of rapamycin

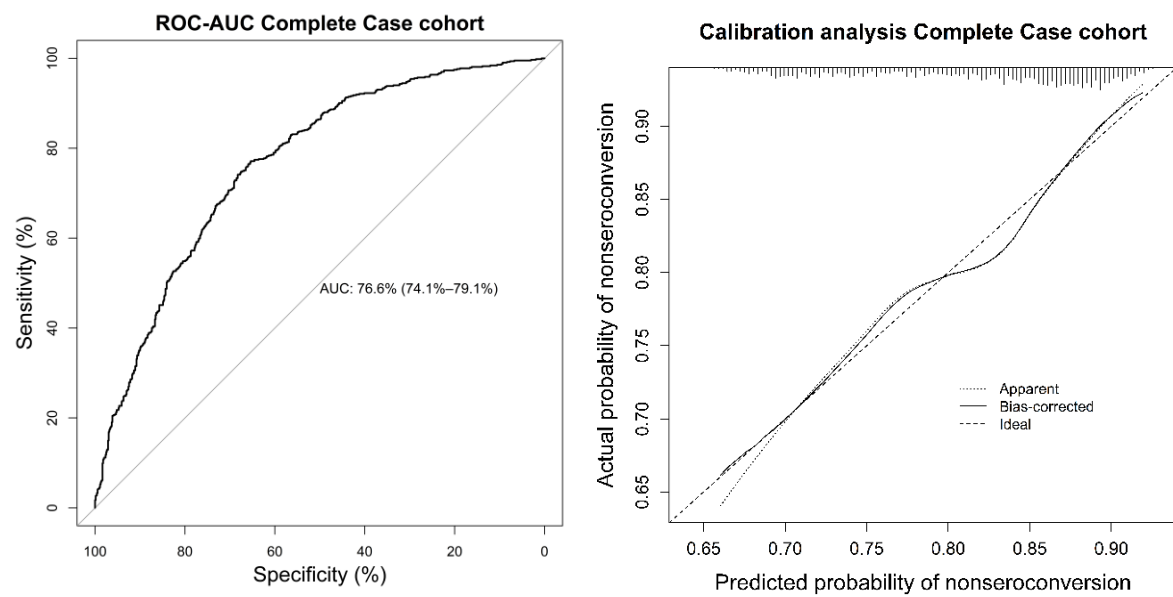


Figure S3. Performance and calibration of the complete case cohort (N=1362).

Abbreviations are: ROC, Receiver Operating Characteristic; AUC, area under the curve

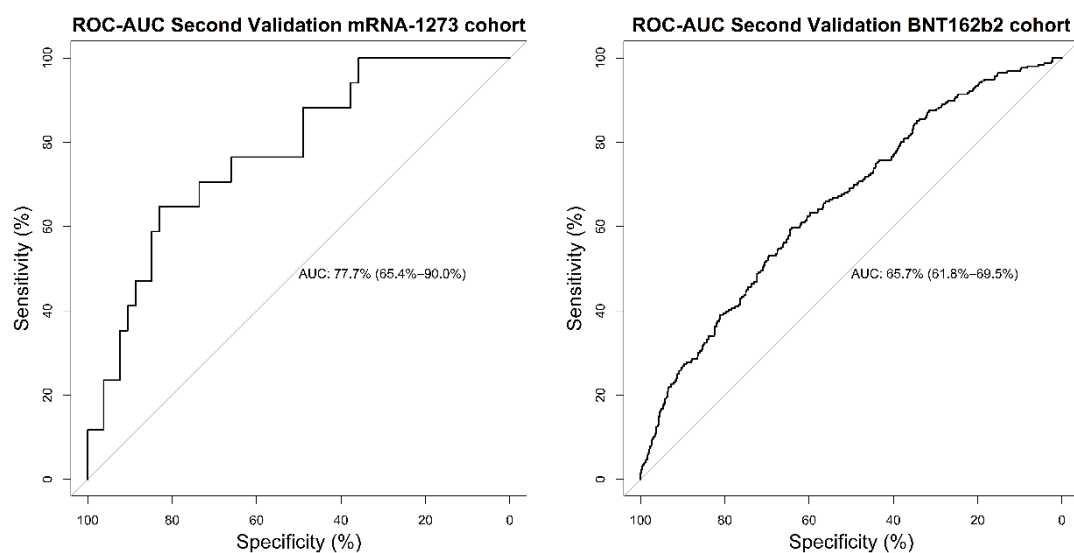


Figure S4. Performance of the final model in KTR who received a third vaccine dose with mRNA-1273 (N=96) or BNT162b2-mRNA (N=1262).

Abbreviations are: ROC, Receiver Operating Characteristic; AUC, area under the curve; mRNA, messenger ribonucleic acid

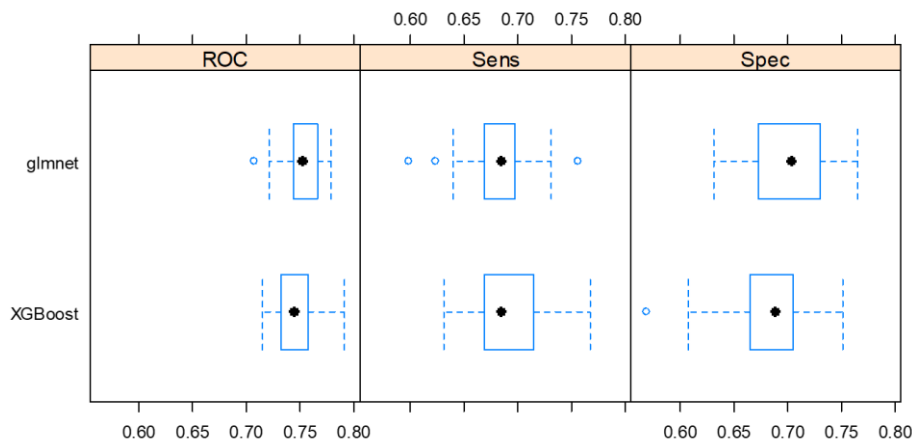
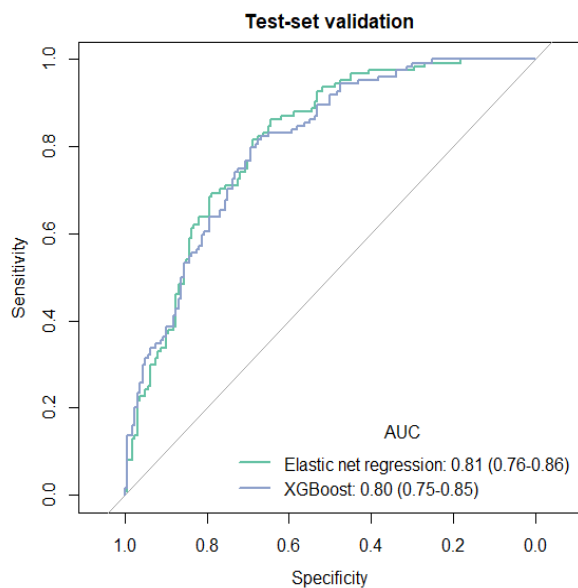
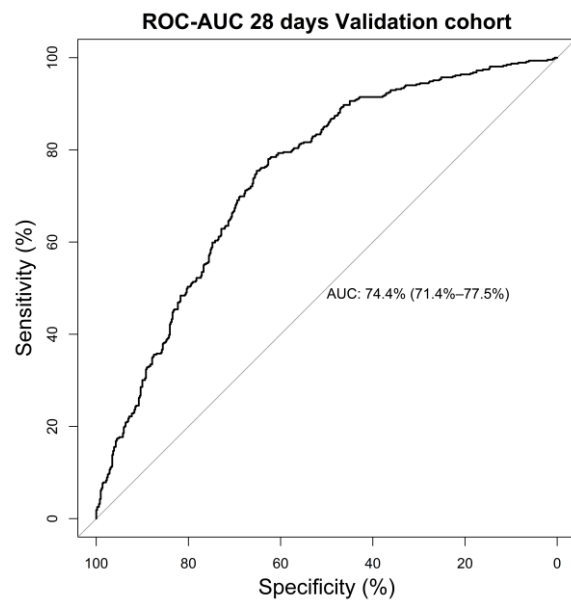
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Figure S5. (A-B) Sensitivity analysis with machine learning. One statistical model with L1-L2 penalization, Elastic-net Generalized Linear Model (GLMnet). One method with Extreme Gradient Boosting (XGBoost). (A) Comparison of 2 models in the discovery set (N=1804) (GLMnet vs XGBoost) after 10 repeats of 4-fold cross-validation. Discrimination of all outer-folds plotted. AUC GLMnet: 0.7534, AUC XGBoost: 0.7454. (B) Discrimination of 2 alternative prediction models (GLMnet vs XGBoost) in the first external validation cohort (N=288). (C) Performance in a cohort including immune response measurements at 28 ± 3 days after the second vaccination (N=989).

Used packages: caret, glmnet, xgboost

Abbreviations are; AUC, area under the curve; ROC, receiver operator characteristics