**Predicting graft outcomes of the kidneys undergoing normothermic machine perfusion before transplantation based on a support vector machine model**

**Abstract**

**Objectives** A significant proportion of kidneys procured from deceased donors are discarded due to concerns of quality. Normothermic machine perfusion (NMP) provides a platform to assess kidney quality prior to transplantation. In this study NMP was used as an assessment tool to investigate the potential of discarded kidneys for transplantation.

**Methods** Data from 41 marginal donor kidneys undergoing NMP before transplantation were used to develop a support vector machine (SVM) prediction model based on donor characteristics and machine perfusion performance. The SVM model was then applied to a series of 15 discarded kidneys undergoing NMP for experimental validation.

**Results** In the training dataset, the SVM model revealed an accuracy of 94.03% (95% CI, 85.41%-98.35%), with a sensitivity of 100% and a specificity of 88.24% in distinguishing between functioning and failed graft. The ROC AUC was 0.914 (95% CI, 0.82-1.00). In the discarded kidney series, 10 kidneys were predicted to have a low probability of graft failure (0.16%-11.70%), while 5 kidneys were predicted to have a high probability of graft failure (16.47%-86.73%). Kidneys predicted to function showed superior glomerular filtration [CrCl at 120min: 4.4 (3.4-4.9) versus 0.6 (0.5-0.7) ml/min/100g, p=0.002], better tubular transportation [TNa at 120min: 557.9 (462.9-681.7) versus 68.3 (50.3-78.1) mmol/min/100g, p=0.003], and higher oxygen utilization efficiency [TNa/VO2 at 120min: 212.5 (173.1-244.9) versus (41.9) mmolNa/mlO2, p<0.001] compared to those predicted to fail.

**Conclusions** This study introduces an SVM model to predict posttransplant graft outcomes based on NMP performance. Although none of the discarded kidneys were transplanted, the model suggests that 67% of the initially declined kidneys could be considered for transplantation.

**Keywords**

Graft survival, kidney transplantation, organ preservation, quality assessment.

**Introduction**

Kidney transplantation is the preferred treatment for end stage renal disease (ESRD).1 Due to the organ shortage, marginal donor kidneys are increasingly being used to enlarge the donor pool.2,3 Despite this effort, a significant proportion of these kidneys are discarded due to concerns of quality and adverse outcomes.2,4 In the Netherlands, between 2015 and 2020, 402 (34%) kidneys from deceased donors were discarded based on subjectively assessed impaired organ quality. Notably, 93 (66%) of the kidneys discarded due to acute kidney injury (AKI) were only in AKI stage I or II.5

Acceptable organ quality is the basis for achieving favorable transplant outcomes. In the context of organ scarcity, it is crucial to improve the utilization of marginal donor kidneys by identifying those eligible for transplantation. Normothermic machine perfusion (NMP), which simulates a physiological environment, has emerged as a promising platform for kidney quality assessment, particularly for evaluating marginal donor kidneys. A previous study introduced an ex vivo kidney perfusion quality assessment score (EVKP score) that facilitated the successful transplantation of five initially declined kidneys based on macroscopic appearance, renal blood flow and urine output during NMP.6,7 However, no studies have explored the potential of developing a prediction model for post-transplant outcomes based on machine perfusion performance.

Machine learning techniques are increasingly being applied to predict graft outcomes in kidney transplantation.8-11 Among these, Support Vector Machine (SVM) stands out for its ability to incorporate non-vector inputs devoid of magnitude or orientation through the use of kernel functions.12 SVM can estimate a hyperplane and determine a decision boundary that maximizes inter-class margins, thereby ensuring precise classification. This capability makes SVM effective in handling high-dimensional datasets and performing non-linear classification tasks.

To our knowledge, this is the first study developing an SVM model based on donor characteristics and kidney machine perfusion performance to predict graft outcomes for marginal kidneys. Additionally, we applied this model to a series of discarded kidneys for experimental validation and to assess their potential for transplantation.

**Materials and methods**

**Study cohort**

This study consists of two cohorts, the clinical transplant series and discarded kidney series.

In the clinical transplant series, data from our clinical NMP program were used to develop the prediction model.13 The kidneys included in this analysis were all from marginal donors—either donation after circulatory death (DCD) or donation after brain death (DBD) donors over 60 years old. The donor kidneys were considered meeting the criteria for transplantation before NMP. These kidneys underwent a 2-hour NMP and then were transplanted. Graft survival was followed up until August 2024. Graft failure was defined as return to dialysis or retransplantation.

In the discarded kidney series, kidneys declined for transplantation within the Eurotransplant Kidney Allocation System (ETKAS) due to concerns of insufficient organ quality were allocated to our center for research purposes. After standard back-table benching, these kidneys underwent a 2-hour NMP. The previously developed prediction model was applied to these kidneys to evaluate the transplantability based on machine perfusion performance. Renal function, injury, and histological changes were assessed for experimental validation.

**Normothermic machine perfusion**

In the clinical transplant series, kidneys were perfused using the Kidney Assist (XVIVO, Groningen, the Netherlands) under sterile conditions in the organ perfusion room. In the discarded kidney series, kidneys were perfused in the laboratory using a similar NMP setup (Harvard Apparatus®, Germany) as previously described.14 This setup operates on the same principle as the clinical one.

In both series, kidneys were perfused with an oxygenated, red blood cell-based solution at 37°C, with a controlled pressure of 70-75 mmHg. In the clinical series, cross-matched red blood cells compatible with the donor were used as the oxygen carrier. In the discarded kidney series, O-negative red blood cells or those matching the donor’s blood group were used. Additional creatinine (90mg, Sigma-Aldrich) was added to the perfusate of discarded kidneys to assess the glomerular filtration rate.

**SVM model development**

The SVM model was developed using donor characteristics and kidney perfusion metrics as predictors. Specifically, donor age, urine protein creatinine ratio (UPCR), one-hour renal blood flow (RBF), and one-hour urine output were included as variables. RBF and urine output were normalized to kidney weight, reported as milliliters per minute per 100 grams (ml/min/100g) and milliliters per 100 grams (ml/100g), respectively.

To address the imbalance in graft outcomes (graft functioning versus graft failure), random oversampling was applied to duplicate instances of the minority class (graft failure). This approach balanced the class distribution, enabling the SVM model trained on the oversampled dataset to provide more reliable predictions across both outcome classifications.

The SVM was implemented using a radial basis function kernel, allowing the model to handle data that is not linearly separable in its original space. The regularization cost parameter was set to 1. To reduce the risk of false positives—incorrectly predicting graft failure when the graft was functioning, the decision threshold was set at 0.7.

**Renal function and injury assessment**

In the discarded human kidney series, RBF was recorded consistently, and urine output was measured hourly during NMP. Perfusate and urine samples were collected at 30, 60 and 120 minutes for further analysis. Oxygen consumption (VO2) was assessed through blood gas analyses. Lactate dehydrogenase (LDH), aspartate aminotransferase (AST), creatinine and sodium concentrations were determined in the hospital biochemistry laboratory using standard clinical assays. Creatinine clearance (CrCl), fractional excretion of sodium (FENa), and total sodium reabsorption (TNa) were calculated using the equations in Table S1.

**Histopathology assessment**

Renal cortex biopsies were taken from each kidney before NMP, fixed in 4% buffered paraformaldehyde, embedded in paraffin, and cut into 5µm sections. Periodic acid-Schiff (PAS) staining was used to evaluate interstitial fibrosis, tubular atrophy, arterial hyalinosis, arterial intimal thickening, and glomerulosclerosis by a renal pathologist (M.C.v.G) blinded to the study. Each type of lesion was scored from 0 (none) to 3 (severe injury) according to the Banff Classification of Allograft Pathology.15

**Statistical analysis**

Data were reported as median with interquartile range (IQR) for continuous variables and numbers and percentages for categorical variables. SVM Model's effectiveness was assessed through a confusion matrix and the area under the receiver operating characteristic (ROC) curve (AUC). We calculated accuracy, positive predictive value (PPV), negative predictive value (NPV), sensitivity, specificity and F1 score based on the matrix. Two-way ANOVA was used to compare renal function and viability markers in the discarded kidney series. Fixed effects were time, group factor, and the interaction of the group factor with time. Individual kidneys were considered as random effects. A Geisser–Greenhouse correction and a restricted maximum likelihood approach were used. We used R (version 4.2.2, R Core Team) and GraphPad Prism (version 9.3.1, GraphPad Software) for statistical analysis and data presentation.

**Results**

**Baseline characteristics**

In the clinical transplant cohort, 41 deceased-donor kidneys eligible for our clinical NMP program were included between May 2021 and April 2024. Patient demographics and perfusion metrics are presented in Table 1. All kidneys underwent 2-hour NMP and then were transplanted by a consistent transplant team. The median follow-up time for patients and grafts was 1.1 years (IQR, 0.5-2.0). There were 23 cases of delayed graft function (DGF) and 4 cases of primary non-function (PNF). By the end of follow-up, 7 grafts had failed due to rejection (n = 3), sepsis (n = 2), renal artery anastomotic stenosis (n = 1), and glomerular sclerosis (n = 1).

In the discarded kidney cohort, 15 kidneys declined for transplantation due to concerns of acute kidney injury (AKI) were offered to our center for research between March 2023 and March 2024. Donor characteristics are presented in Table 2. The median donor age was 63 (IQR, 47-73) years, with 7 DCD donors, and 8 DBD donors. Terminal serum creatinine levels was 140 (91-162) μmol/l. UPCR was 47.6 (34.6-77.7) mg/mmol. The kidneys were classified as AKI stage I (n=8), II (n=6), and III (n=1). The warm ischemia time (WIT) for DCD donors was 18 (15-21) minutes, and cold ischemia time (CIT) was 12.7 (9.3-23.8) hours.

**SVM model development**

The transplant cohort was oversampled to create a dataset comprised 34 instances of functioning graft and 33 instances of graft failure. The predictive performance of the SVM model, based on on donor age, UPCR, RBF and urine output, is summarized in Table 3. The confusion matrix revealed an accuracy of 94.03% (95% CI, 85.41%-98.35%). The model demonstrated a sensitivity of 100% and a specificity of 88.24%. The PPV was 89.19%, and the NPV was 100%, indicating the model's strength in accurately identifying functioning grafts. The ROC AUC was 0.914 (95% CI, 0.82-1.00), suggesting a high level of model reliability and an capability in distinguishing between functioning and failed grafts under varied threshold settings (Figure 1).

**Discarded kidney series**

The SVM model, trained to predict graft failure, was applied to the discarded kidney series. Figure 2 shows the distribution of predicted probabilities of graft failure by the SVM model. Ten kidneys were predicted to have a low probability of graft failure (0.16%-11.70%), while 5 kidneys were predicted to have a high probability of graft failure (16.47%-86.73%).

**Renal function during NMP**

The discarded kidneys were categorized into functioning and failure groups based on the SVM model predictions. Compared to kidneys predicted to fail, those predicted to function demonstrated superior glomerular filtration [CrCl at 120min: 4.4 (3.4-4.9) versus 0.6 (0.5-0.7) ml/min/100g, p=0.002], better tubular transportation [TNa at 120min: 557.9 (462.9-681.7) versus 68.3 (50.3-78.1) mmol/min/100g, p=0.003], and higher oxygen utilization efficiency [TNa/VO2 at 120min: 212.5 (173.1-244.9) versus (41.9) mmolNa/mlO2, p<0.001, Figure 3A-C]. Kidneys in the functioning group also showed a trend of lower FENa, higher demand of oxygen, and urine output than those in the failure group (Figure 3D-F).

**Renal injury measurement**

As general injury markers, levels of LDH and AST were slightly higher in kidneys predicted to fail compared to those predicted to function (Figure 3G, H).

Representative histopathological images are shown in Figure 4A. Most kidneys exhibited mild to moderate injury across the five assessed criteria. No significant differences in pathological changes were observed between the functioning and failure groups (Figure 4B). Detailed scores for each kidney are provided in Table S2.

**Discussion**

We developed an SVM model based on donor characteristics and kidney NMP performance to predict graft status posttransplant. When applied to a series of discarded kidneys, the model predicted that 67% of the initially declined kidneys would function if transplanted. This prediction was further supported by superior renal function and viability observed during NMP. Our findings may assist in decision-making (e.g. kidney transplantability) and increase the utilization of marginal donor kidneys.

Several studies have previously reported to predict graft outcomes using machine learning techniques or traditional regression models. Naqvi et al.16 developed a machine learning model based on 37 donor and recipient characteristics, using a large dataset of over 50000 kidney transplants, to predict allograft status. Similarly, a risk prediction score (iBox) was developed using data from multiple international cohorts of 7557 participants, which achieved accurate calibration and discrimination in predicting long-term graft failure (C-index 0.81, 95% CI 0.79 to 0.83).17 However, these models primarily rely on data obtained posttransplant, limiting their utility in assessing the transplantability of donor kidneys before transplantation occurs.

Our approach differs by focusing on developing a prediction model that can determine a donor kidney’s suitability for transplantation before the procedure, potentially reducing the unnecessary discard of viable organs. Similarly, Senanayake et al.18 introduced a Cox regression model based on pretransplant donor and recipient characteristics, which achieved a C-index of 0.67 in discriminating death-censored graft failure. While their study aims to match eligible donor kidneys to the most suitable recipients, our rational is to identify functional donor kidneys that have been initially considered unsuitable for transplantation based on subjective assessments.

In the training set consisting of 41 kidney NMP and transplanttaion cases, our SVM model correctly identified all graft failure cases and majority of the functioning kidneys. In the test set, we identified 10 of the initially discarded kidneys as potentially eligible for transplantation, all of which were classified as AKI stage I (n = 5) or II (n = 5). AKI kidneys are discarded at a significantly higher rate than those without AKI due to concerns about acute rejection and risks of graft failure.19-22 However, research from diverse data sources has shown that recipients of AKI kidneys can achieve long-term graft survival comparable to that of non-AKI kidneys.23-29 Reese et al. found no significant associations between donor-derived AKI and biopsy-proven acute rejection, suggesting that immunological complications can be successfully managed in AKI-affected kidneys.23 Liu et al. examined a national US cohort of 6722 deceased donors with AKI and found that although AKI kidneys were more likely to develop DGF, their graft survival rates were comparable to those of non-AKI kidneys.24 Boffa et al. reported that PNF rates were only significantly higher for AKI stage III kidneys.28 This implies that discarding kidneys from donors with AKI, especially those with stage I or II, may be unwarranted, and these kidneys could contribute positively to the donor pool.

Another practical question is identifying suitable transplant candidates for marginal kidneys. Some studies recommend allocating these kidneys to older candidates to better match the life expectancy of organs and recipients, which has been successfully implemented by the Eurotransplant Senior program and demonstrated favorable 5-year outcomes.30 On the other hand, Bae and colleagues31 used a random forests algorithm to predict posttransplant graft survival based on the Kidney Donor Profile Index (KDPI) and Estimated Post-Transplant Survival (EPTS). Their findings show that KDPI has minimal impact among candidates with low EPTS, suggesting that candidates in good overall condition (e.g., with less dialysis time) can better tolerate the marginal graft function expected with a lower-quality allograft. The most important is that the individual candidate would obtain survival benefit from kidney transplantation with a marginal kidney. Candidate’s own perspectives on how much survival benefit is sufficient to justify the surgical stress, life-long immunosuppression, and financial burden associated should be considered.31

Currently, our SVM model relies on one-hour perfusion parameters. The optimal duration for kidney NMP remains unclear. Although studies have explored the feasibility of normothermic preservation for up to 24 or 48 hours, prolonged NMP may induce endothelial injury, resulting in adverse consequences after transplantation.32-34 Therefore, a one-hour NMP duration might be acceptable for determining a kidney’s suitability for transplantation, considering the potential risks of injury and current clinical practice.35-37 However, we anticipate that with continuous advancements in machine perfusion technology, NMP may not only assess organ quality but also recondition and repair the organ. Marginal kidneys are likely to benefit from extended preservation with therapeutic interventions. Further research is warranted to investigate the necessity of prolonged NMP for organ quality assessment and its potential in improving organ quality.

Our study has some limitations to be addressed. Firstly, the study is limited by its reliance on data from single center with a small group size, which restricts the variables that are included in the prediction model and the generalizability of our findings. A larger and multi-center cohort could enhance the validity of our prediction model. Secondly, we used experimental validation since the discarded kidneys were not intended for transplantation, which limits the robustness of our findings. Thirdly, we were only able to predict binary outcomes (graft failure or not) within a relatively short period and were unable to predict time-to-event (survival) outcomes.

**Conclusion**

Our study introduced an NMP-based SVM model to predict graft outcomes after kidney transplantation. Although none of these discarded kidneys were transplanted, the data suggest that 67% of these kidneys should be considered for transplantation.

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Table 1. Donor and recipient characteristics in clinical transplant series

|  |  |
| --- | --- |
| **Donor (N = 41)** |  |
| Age (year) | 65 [58-72] |
| Sex, male | 31 (76%) |
| Cause of death |  |
| CVA | 16 (39%) |
| Trauma | 7 (17%) |
| Cardiac arrest | 14 (34%) |
| Others | 4 (10%) |
| Donor type |  |
| DCD | 30 (73%) |
| DBD | 11 (27%) |
| Terminal serum creatinine (μmol/l) | 64 [55-94] |
| Urinary protein (g/l) | 0.21 [0.11-0.38] |
| UPCR (mg/mmol) | 24.3 [18.6-36.1] |
| First WIT (minutes)\* | 16 [13-18] |
| **Recipient (N = 41)** |  |
| Age (year) | 67 [60-72] |
| Sex, male | 30 (73%) |
| HLA mismatches |  |
| 0-1 | 4 (10%) |
| 2-4 | 22 (54%) |
| 5-6 | 15 (37%) |
| CIT (hours) | 9.5 [7.1-11.6] |
| Second WIT (minutes) | 20 [17-25] |
| **Perfusion metrics** |  |
| 1h RBF (ml/min/100g) | 186 [149-221] |
| 2h RBF (ml/min/100g) | 210 [151-263] |
| 1h urine output (ml/100g) | 62 [28-110] |
| 2h urine output (ml/100g) | 78 [38-174] |

Descriptive statistics use median [IQR] for continuous variables and numbers (%) for discrete variables. CIT, cold ischemia time; CVA, cerebrovascular accident; DBD, donation after brain death; DCD, donation after circulatory death; HLA, human leukocyte antigens; RBF, renal blood flow; UPCR, urine protein creatinine ratio; WIT, warm ischemia time.

\*Only applicable for DCD donors.

Table 2. Donor characteristics in the discarded human kidney series (N = 15)

|  |  |
| --- | --- |
| Age (year) | 63 [47-73] |
| Sex, male | 12 (80%) |
| Cause of death |  |
| CVA | 5 (33%) |
| Trauma | 4 (27%) |
| Cardiac arrest | 4 (27%) |
| Others | 2 (13%) |
| Donor type |  |
| DCD | 7 (47%) |
| DBD | 8 (53%) |
| Terminal serum creatinine (μmol/l) | 140 [91-162] |
| Urinary protein (g/l) | 0.59 [0.35-0.87] |
| UPCR (mg/mmol) | 47.6 [34.6-77.7] |
| AKI classification |  |
| I | 8 (53%) |
| II | 6 (40%) |
| III | 1 (7%) |
| First WIT (minutes)\* | 18 [15-21] |
| CIT (hours) | 12.7 [9.3-23.8] |
| **Perfusion metrics** |  |
| 1h RBF (ml/min/100g) | 177 [140-189] |
| 2h RBF (ml/min/100g) | 201 [163-225] |
| 1h urine output (ml/100g) | 12 [7-23] |
| 2h urine output (ml/100g) | 23 [14-40] |

Descriptive statistics use median [IQR] for continuous variables and numbers (%) for discrete variables. AKI, acute kidney injury; CIT, cold ischemia time; CVA, cerebrovascular accident; DBD, donation after brain death; DCD, donation after circulatory death; UPCR, urine protein creatinine ratio; WIT, warm ischemia time.

\* Only applicable for DCD donors.

Table 3. Diagnostic performance of the SVM model to predict graft failure based on NMP parameters

|  |  |
| --- | --- |
| Metrics |  |
| Accuracy | 94.03% |
| Precision (PPV) | 89.19% |
| NPV | 100% |
| Recall (Sensitivity) | 100% |
| Specificity | 88.24% |
| F1 score | 94.29% |
| AUC | 0.914 (0.820-1.000) |

NPV, negative predictive value; PPV, positive predictive value.

A graph of a function

Description automatically generated

Figure 1. Diagnostic accuracy of the SVM model for graft failure in the transplant kidney series

A graph with a blue line

Description automatically generated

Figure 2. Histograms and density plot to predict graft failure in the discarded kidney series. The histogram (gray bars) on the left Y-axis represents the frequency of predictions across different probability intervals, and the density plot (blue line) on the right Y-axis represents the distribution of these probabilities.

A graph of different sizes and shapes

Description automatically generated with medium confidence

Figure 3. Renal function and injury makers during NMP. (A) Creatinine clearance (CrCl, ml/min/100g); (B) total sodium reabsorption (TNa, mmol/min/100g); (C) oxygen utilization efficiency (TNa/VO2, mmolNa/mlO2); (D) fractional excretion of sodium (FENa, %); (E) oxygen consumption (VO2, mlO2/min/100g); (F) urine output (ml/h); (G) lactate dehydrogenase (LDH, U/L) and (H) aspartate aminotransferase (AST, U/L). Data presented as median with interquartile range. \*p<0.05, \*\*p<0.01, \*\*\*p<0.001.

A close-up of a tissue

Description automatically generated

Figure 4. (A) Representative morphological images of kidneys predicted to function (left) and fail (right). (B) Histological scores of PAS-stained biopsies ranging from 0 (none) to 3 (severe injury). The parameters assessed include interstitial fibrosis (IF), tubular atrophy (TA), arterial hyalinosis (AH), arterial intimal thickening (AIT) and glomerulosclerosis (GS).

Table S1. Equations for calculating renal function

|  |  |  |
| --- | --- | --- |
| Parameter | Equation | Abbreviations |
| Creatinine clearance (CrCl, ml/min/100g) |  | UCr, urine creatinine concentration (mmol/L)  U, urine output rate (mL/min)  PCr, perfusate creatinine concentration (mmol/L)  g, kidney weight (gram) |
| Fractional excretion of sodium (FENa, %) |  | UNa, urine sodium concentration (mmol/L)  PNa, perfusate sodium concentration (mmol/L)  PCr, perfusate creatinine concentration (mmol/L)  UCr, urine creatinine concentration (mmol/L) |
| Oxygen consumption (VO2, mlO2/min/100g) |  | Hb, hemoglobin concentration (mmol/L)  pO2, partial oxygen pressure (kPa)  K, solubility constant of oxygen in water at 37°C that equals 0.0225 (mLO2 per kPa)  SO2, saturation (%)  Q, renal blood flow (dL/min)  g, kidney weight (gram) |
| Total sodium reabsorption (TNa, mmol min/100g) |  | PNa, perfusate sodium concentration (mmol/L)  UNa, urine sodium concentration (mmol/L)  U, urine output rate (mL/min)  g, kidney weight (gram) |

Table S2. Pathological scores of the kidneys in the discarded series

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Predicted status | IF | TA | AH | AIT | GS |
| K1 | Functioning | 0 | 0 | 0 | 0 | 2 |
| K2 | Failure | 1 | 1 | 1 | 0 | 2 |
| K3 | Functioning | 0 | 1 | 1 | 1 | 2 |
| K4 | Functioning | 0 | 0 | 0 | 0 | 1 |
| K5 | Functioning | 0 | 0 | 1 | 0 | 0 |
| K6 | Functioning | 1 | 1 | 1 | 0 | 3 |
| K7 | Functioning | 1 | 1 | 1 | 2 | 2 |
| K8 | Functioning | 0 | 1 | 2 | 0 | 0 |
| K9 | Functioning | 0 | 1 | 2 | 3 | 2 |
| K10 | Functioning | 2 | 2 | 2 | 2 | 2 |
| K11 | Functioning | 1 | 1 | 2 | 1 | 0 |
| K12 | Failure | 2 | 2 | 1 | 2 | 3 |
| K13 | Failure | 0 | 1 | 1 | 0 | 0 |
| K14 | Failure | 0 | 1 | 1 | 0 | 1 |
| K15 | Failure | 0 | 0 | 0 | 0 | 0 |

AH, arterial hyalinosis; AIT, arterial intimal thickening; GS, glomerulosclerosis; IF, interstitial fibrosis; PAS, periodic acid-Schiff; TA, tubular atrophy.