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Walking Ability and Brain Natriuretic Peptide Are Highly Predictive of Kidney Transplant Waiting List Removal

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Background: Kidney transplant waitlist management is complex because waiting time is long, and the patients have significant comorbidities. Identification of patients at highest risk for waiting list removal for death and medical complications could allow better outcomes and allocation of resources. **Methods:** Demographics, functional and frailty assessment, and biochemical data were retrospectively analyzed on 313 consecutive patients listed for kidney transplant. Troponin, brain natriuretic peptide, components of the Fried frailty metrics, pedometer activity, and treadmill ability were measured at the time of transplant evaluation and at subsequent re-evaluations. Cox proportional hazards models were used to identify factors associated with death or waiting list removal for medical reasons. Multivariate models were created to identify significant predictor sets. **Results:** Among 249 patients removed while waitlisted, 19 (6.1%) died and 51 (16.3%) were removed for medical reasons. Mean follow-up duration was 2.3 y (±1.5 y). 417 sets of measurements were collected. Significant ($P < 0.05$) non–time-dependent variables associated with the composite outcome identified on univariate analysis included *N*-terminal probrain natriuretic peptide (BNP), treadmill ability, pedometer activity, diagnosis of diabetes and the Center of Epidemiological Studies Depression Scale question asking how many days per week could you not get going. Significant time-dependent factors included BNP, treadmill ability, Up and Go, pedometer activity, handgrip, 30 s chair sit-stand test, and age. The optimal time-dependent predictor set included BNP, treadmill ability, and patient age. **Conclusions:** Changes in functional and biochemical markers are predictive of kidney waitlist removal for death and medical reasons. BNP and measures of walking ability were of particular importance. (Transplantation Direct 2023;9: e1483; doi: 10.1097/TXD.0000000000001483.)

Kidney transplant waiting times are long, exceeding 5 y in many programs.[1] US programs have on average over 400 waitlisted patients and 9% of programs manage over 1000 listed patients.[2] Simultaneously, as outcomes have improved, transplant selection has been expanded to include older and more medically complex patients.[1] Also, attrition among chronic renal failure patients is inherently high.[3] For these reasons, ensuring patients' continued suitability for transplant is challenging and programs expend considerable effort on waitlist management.

Frailty and functional metrics are associated with pretransplant and posttransplant outcomes including waiting list and

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transplant access, posttransplant length of stay, and patient survival.[4–10] A quarter of waitlisted patients become more frail while waitlisted and subsequently have worse outcomes.[11] When incorporated into waitlist management strategies, functional metrics have been shown to improve predictiveness of waitlist survival.[12] Therefore, programs have begun including functional assessments in pretransplant management.[13]

In our Veterans Affairs (VA) kidney transplant program, waiting time exceeds 4 y, and most of our patients travel more than 500 miles for evaluation. We seek to perform routine in-person evaluation updates at regular intervals. However, performing re-evaluations consumes resources and utilizes clinic time that could be spent evaluating new referrals.

Despite recommendations to use functional testing to improve candidate selection and refine the re-evaluation process, most centers do not collect these metrics, and it remains unclear which metrics best correlate with waiting list outcomes.[13] Since 2015, we have collected a set of frailty, functional, and cardiac biochemical markers at the time of evaluation and re-evaluation. These include components of the Fried metrics such as the chair sit-stand test that have been previously correlated with pretransplant outcomes, troponin and brain natriuretic peptide that have been associated with posttransplant survival, and pedometer and treadmill testing that we have previously shown to correspond with candidate selection.

To better understand whether our collected metrics could be used to triage our re-evaluation process this study sought to (1) evaluate the association of functional, frailty and biochemical markers at the time of evaluation with waitlist outcomes, (2) evaluate which of the metrics measured over time most correlated with waitlist removal or improved initial predictiveness, and (3) evaluate whether metrics grouped together improved prediction of outcomes.

MATERIALS AND METHODS

Study Population

Following Institutional Review Board approval through the Iowa City VA Health Care System and University of Iowa, we performed a retrospective analysis of patients listed for transplant following initial[4] or follow-up evaluation between January 1, 2015, and December 31, 2018. Outcomes were censored as of November 20, 2021. Follow-up visits were either routine or following a change in health status (nonroutine).

Basic demographic factors that were abstracted from the medical records included patient age, sex, race (as self-reported to and categorized by the VA), body mass index (BMI), history of hypertension and diabetes, primary cause of renal failure, and length of time on dialysis. The same biochemical tests and frailty assessments were collected on all patients at the time of the initial on-site evaluation and all follow-up appointments as described below.

Outcome Assessment

Waitlist outcomes included delisting for transplant, medical reasons, psychosocial reasons, death, and remaining on the waitlist. Reasons for delisting (other than death) were obtained from the charted listing conference notes that described consensus decisions of the listing committee. When delisting included both medical and psychosocial reasons, the outcome was recorded as a medical delisting. The primary outcome of interest was a composite endpoint of delisting for medical reasons or death. The primary objectives of this study were to identify factors associated with delisting for medical reasons or death from the time of listing and quantify those relationships.

Biochemical and Frailty Factors Assessed at the Time of On-Site Transplant Evaluation and Follow-up

Biochemical Markers

Blood for biochemical tests was drawn before functional tests. Cardiac troponin T and *N*-terminal probrain natriuretic peptide (BNP) drawn at the time of evaluation were immunoassayed in our clinical laboratory using electrochemiluminescence on a Roche Cobas 6000 analyzer (Roche Diagnostics, Indianapolis, IN). The troponin T reference range was <0.03 ng/mL, with a critical level defined as >0.09 ng/mL. BNP reference ranges were age (by decade) and sex adjusted. For males and females respectively, the 95th percentile for BNP levels in pg/mL were as follows: ages 45–54, 138, and 192; ages 55–64, 177, and 226; ages 65–74, 229, and 353; and ages ≥75, 852, and 624.

Frailty Metrics

Four functional metrics were collected including handgrip, 30 s chair sit-stand, chair sit-reach, and timed Up and Go. Each metric was measured as previously described.[14–16] Briefly, handgrip was measured in kilograms on a calibrated Jamar Dynamometer (JLW Instruments, Chicago, IL) in the right and left hands and a mean value was calculated.[17] The number of times that a patient rose to the full standing position within a 30-s period was recorded in the sit-stand test. For the sit and reach test, the gap in centimeters between the middle fingertip and toes of an extended leg was measured with the patient reaching with both arms extended, in the seated position, at the edge of the chair. Ability to touch the toes or go beyond was recorded as zero. In the Up and Go test, the patient was timed while proceeding as quickly as possible from the seated position around a cone positioned 8 feet from the chair and returning to the seated position.

Two self-reported answers to questions from the Center of Epidemiological Studies Depression Scale (CES-D) measuring level of exhaustion were recorded. These included in how many days in the past week (0–7 d) (a) was everything you did an effort, and (b) could you not get going?[18]

Treadmill and Pedometer Testing

Treadmill, pedometer, functional, and frailty measurements were made on nondialysis days (in the case of hemodialysis) or before dialysis if conducted on a dialysis day.

Symptom limited treadmill testing was performed on a GE Health Care T-2100 treadmill (GE Medical Systems, Milwaukee, WI) according to the modified Bruce or Naughton protocols as previously described.[19] Early in the data collection phase, the modified Bruce or Naughton was used, but with experience we evolved to exclusively use the Naughton protocol because we found that its more graded acceleration into stress gave the renal failure patients a better opportunity to achieve their maximal plateau. Treadmill data that were recorded included maximal metabolic equivalents (METS) level achieved, total time on treadmill, and reason for stopping the test. For this analysis only METS level was analyzed.

An EKHO Two pedometer (EKHO; Dallas, TX) was calibrated for each patient per manufacturer instructions. Patients were instructed to wear the pedometer all the time while awake. Pedometer "on" and "off" times were recorded. These data were measured as steps taken and calculated steps per time.

Statistical Analysis

Summary statistics were calculated for patient demographics, functional, and frailty metrics using the full sample, as well as for the subgroups "transplanted or remaining on the waitlist" and "removed for death or medical reasons." To compare patients with and without follow-up visits, additional summary statistics were calculated for patient demographics, functional, and frailty metrics for patient subgroups "no follow-up," "all follow-up" (all patients receiving a follow-up visit regardless of reason), "routine," and "nonroutine" follow-up. Categorical measures are presented as counts and percentages. Distributions for continuous measures were assessed for normality and are reported as means and standard deviations or medians and interquartile ranges (IQR). Univariate logistic regression analysis was performed to assess which variables were associated with "nonroutine" follow-up visits. Estimates and 95% confidence intervals (CIs) are reported, along with *P* values.

Univariate Cox proportional hazards models were fit to identify which patient characteristics and frailty metrics associate with time to death or medical delist. This modeling approach incorporated time-varying covariates to update measure values for patients with multiple visits over their observation time. Point and interval estimates for delist hazard ratios (HRs) were calculated for predictors, along with their *P* values. After assessing the significance of each univariate predictor, we utilized a backward multivariate model selection procedure to identify the optimal covariate set and assess the adjusted estimates for the included measures. We set the significance cutoff for inclusion in the final multivariate model at $P \leq 0.1$. Because our goal is identification of factors, rather than evaluation, minimization of type II errors is more important than type I.

As a sensitivity analysis, we constructed a similar series of univariate and multivariate regression models using the logistic regression framework with repeated measures for multiple patient visits. This approach removes the temporal component to assess the effect of patient characteristics and frailty metrics on the likelihood of death or medical delist. Point and interval estimates for delist odds ratios (ORs) were calculated for predictors, along with their *P* values. A similar backward selection procedure was conducted using a significance cutoff for inclusion in the final multivariate model at $P \leq 0.1$ to identify related factors.

Two final models were identified for reporting:

1. The optimal covariate set identified using a backward model selection procedure using Cox proportional hazards modeling starting with all predictors.
2. The optimal covariate set identified using a backward model selection procedure using logistic regression starting with all predictors.

Although the backward model selection procedure can lead to spurious predictors, our goal is to identify informative measures about the risk of patient death or medical delist. As such, we feel this inclusive approach provides more potential information useful for future investigation. Figures with contour lines representing propensity scores for different patient characteristic profiles were constructed to provide a clearer idea of how these measures affect a patient's likelihood of a negative outcome on the transplant waitlist.

RESULTS

Study Population

Among the consecutive 313 listed patients, 249 patients (79.6%) were removed from the waitlist: 162 (51.8%) were transplanted, 19 (6.1%) died, 51 (16.3%) were removed for medical reasons, and 17 (5.4%) were removed for social or nonmedical reasons. Cardiopulmonary issues were the most common reason for waitlist removal (23 patients) and accounted for most of the deaths. The following 2 most common causes of waitlist removal for medical reasons were cancer and functional decline (Table 1). Waitlist removals for reasons other than medical reasons and death were not included in the analysis and were due to patient request usually because of listing at another center (8 patients), followed by nonadherence issues (5 patients), loss of support person (3 patients), and use of illicit substances (1 patient).

The mean age at evaluation was 59.9 y. Ninety-five and a half percent were male, 97.1% were treated for hypertension, 57.2% were diabetic, 65.5% were White, 30.4% were Black or of African descent, and 4.2% other. The mean BMI was 29.5 (Table 2, demographics).

The median length of time on dialysis at the time of first evaluation was 1.95 y. The cause of renal failure was diabetes (139), hypertension (47), focal and segmental glomerulosclerosis (31), polycystic disease (24), and others (72). Ninety-seven (31.0%) patients were not yet on dialysis at the time of the first evaluation. Of these patients approaching dialysis, 65 started dialysis while on the waiting list.

Functional and Frailty Measures

At the time of listing, the median troponin and BNP were 0.02 and 1330, respectively. The median number of steps taken per day as recorded by pedometer was 3740 (IQR: 2340–5560) and mean treadmill ability was 5.9 ± 2.2 METS. Mean hand grip was 31.0 ± 10.7 kg. Median 30-s chair sit-stand was 15.5 repetitions, median chair sit-reach was 0 (IQR: 0–6) cm, and median Up and Go was 5.0 (IQR: 4.2–6.0) s. Over half of patients answered they never felt that everything

TABLE 1.

Causes of waiting list removal for medical reasons

Cause	Nonmortality delist	Mortality delist
Cardiac	14	9
Infection		2
Cancer	9	
Functional decline	9	
Peripheral vascular disease progression	8	
Trauma		2
Neurologic	3	
Other	8	3
Unknown		3
Total	51	19

TABLE 2.

Demographic, biochemical, and functional metrics stratified by waitlist outcome at time of initial listing

	All patients	Transplanted or remaining on the waitlist	Removed from the waitlist for death or medical reasons
N	**313**	**226**	**70**
Demographics			
Age, y[a]	59.9 (9.6)	59.3 (10.0)	62.3 (8.5)
Sex male	299 (95.5%)	216 (95.6%)	66 (94.3%)
Race			
Black	95 (30.4%)	69 (30.5%)	23 (32.9%)
White	205 (65.5%)	148 (65.5%)	44 (62.9%)
Other	13 (4.2%)	9 (4.0%)	3 (4.3%)
Diabetes	179 (57.2%)	119 (52.6%)	50 (71.4%)
Hypertension	304 (97.1%)	220 (97.4%)	67 (95.7%)
Time on dialysis, y[b]	1.95 (0.72–3.64)	1.94 (0.71–3.67)	2.38 (0.92–3.53)
BMI[a]	29.5 (4.1)	29.5 (4.2)	29.6 (3.9)
Biochemical and functional metrics			
Troponin, ng/mL[b]	0.02 (0.01–0.07)	0.02 (0.01–0.06)	0.05 (0.02–0.09)
BNP, pg/mL[b]	1330 (440–3140)	1160 (400–3010)	3370 (1170–12 600)
METS[a]	5.9 (2.2)	6.2 (2.1)	4.9 (2.0)
Steps per day (per 1000)[b]	3.74 (2.34–5.56)	3.71 (2.34–5.57)	2.43 (1.06–3.79)
Hand grip, kg[a]	31.0 (10.7)	31.7 (10.7)	28.5 (9.7)
30-s Sit-Stand[a]	15.5 (6.1)	15.9 (6.1)	13.9 (6.4)
Sit-reach, cm[b]	0 (0–6)	0 (0–6)	0 (0–9)
Up and Go, s[b]	5.0 (4.2–6.0)	5.0 (4.2–6.3)	5.6 (4.7–7.3)
Everything an effort, d/wk[b,c]	0 (0–1)	0 (0–2)	0 (0–2)
Could not get going, d/wk[b,c]	0 (0–0)	0 (0–0)	0 (0–1)
Lost 10 lb, yes/no	96 (31.4%)	70 (31.1%)	28 (41.2%)

[a] Mean (SD).
[b] Median (IQR: Q1–Q3).
[c] Patients were asked 2 CES-D questions: how many days in the past week (0–7 d) (a) was everything you did an effort, and (b) could you not get going? Results are reported according to whether the patient answered that they had no versus one or more days per week where everything was an effort, or they could not get going.
BMI, body mass index; BNP, *N*-terminal probrain natriuretic peptide; CES-D, Center of Epidemiological Studies Depression Scale; METS, metabolic equivalents.

they did was an effort, and over 75% said they never had trouble getting going (Table 2, biochemical and functional metrics). Demographic, biochemical, and functional metrics are compared between transplanted and patients remaining on the waiting list and those removed for death and medical reasons in (Table 2).

Waiting List Removal

Logistic regression analysis was performed using the full sample to assess non–time-dependent associations of variables with waitlist removal for death or medical reasons. Significant factors identified on univariate analysis of demographic, frailty, and functional factors measured at the time of initial evaluation included BNP (OR = 1.03 per 1000 pg/mL increase, 95% CI, 1.02-1.05, $P < 0.01$), treadmill ability (OR = 0.81 per METS point increase, 95% CI, 0.7-0.91, $P < 0.01$), pedometer activity (OR 0.80 per 1000 steps/d increase, 95% CI, 0.71-0.91, $P < 0.01$), number of days you could not get going (comparing 0 with more than 1 d per week patient could not get going) (OR = 1.79, 95% CI, 1.09-2.93, $P = 0.02$), and diagnosis of diabetes (OR = 1.69, CI, 1.04-2.77, $P = 0.04$) (Table 3).

To assess the significance of variables over time, Cox proportional hazard analysis was performed. Significant time-dependent factors included BNP (HR = 1.03 per 1000 pg/mL increase, CI, 1.02-1.05, $P < 0.01$), treadmill ability (HR = 0.75 per METS point increase, CI, 0.66–0.86, $P < 0.01$), Up and Go (HR = 1.16 per second increase, CI, 1.08-1.24, $P < 0.01$), pedometer activity (HR = 0.81 per 1000 steps/d increase, CI, 0.71-0.93, $P < 0.01$), handgrip (HR = 0.98 per kg increase, CI, 0.96-0.99, $P = 0.01$), 30-s chair sit-stand test (HR = 0.93 per second increase, CI, 0.89-0.98, $P < 0.01$), and age (HR = 1.03 per year, CI, 1.00-1.06, $P = 0.03$) (Table 3).

Variables that were not significantly associated with delisting for medical reasons or death in either logistic or Cox analysis included sex, race, hypertension, BMI, troponin, sit-reach, the CES-D questions measuring the number of days per week the patient felt that everything was an effort, and weight loss.

Follow-up

The 313 patients contributed 452 visit observations over the study period. The average duration of follow-up was (mean ± SD) 2.3 ± 1.5 y. One hundred fourteen patients had 2 sets, 23 patients had 3 sets, and 2 patients had 4 sets of measurements collected over the study period. The median (IQR) for the intervals between the first and second, second and third, and third and fourth visits were the following, respectively: 735 (418–847), 470 (363–666), and 559 (531–587) d. To further characterize the patients, they were divided into groups without further follow-up, and those with follow-up that was either routine or nonroutine for a specific reason (Table 4). Among the 139 patients with follow-up visits, 92 were routine and 47 were nonroutine. Odds that a nonroutine follow-up would occur was associated with presence of diabetes, rising BMI, BNP, and worsening pedometer, treadmill, Up and Go, and sit-stand results (Table 5).

TABLE 3.

Univariate analysis of variables associated with waitlist removal for death or medical reasons compared with remaining on the waitlist

	Logistic regression analysis				Cox time to event modeling			
Patient characteristics	**Odds ratio**	**95% Lower CI**	**95% Upper CI**	***P* value**	**Hazard ratio**	**95% Lower CI**	**95% Upper CI**	***P* value**
Age, y (SD)	1.01	0.99	1.035	0.33	1.03	1.00	1.06	**0.03**
Sex (male)	0.97	0.36	2.61	0.94	0.83	0.30	2.31	0.72
Race								
Black	1.011	0.62	1.64	0.96	0.93	0.57	1.50	0.76
White								
Other								
Diabetes (yes/no)	1.69	1.04	2.77	**0.04**	1.65	0.98	2.77	0.06
Hypertension (yes/no)	0.88	0.26	3.05	0.84	0.74	0.25	2.20	0.59
BMI (per BMI point increase)	1.00	0.94	1.05	0.88	1.00	0.95	1.06	0.98
Troponin (per ng/mL)	1.02	0.94	1.12	0.63	1.01	0.95	1.08	0.69
BNP (per 1000 pg/mL increase)	1.03	1.02	1.05	**<0.01**	1.03	1.02	1.05	**<0.01**
METS (per MET point)	0.81	0.72	0.91	**<0.01**	0.75	0.66	0.86	**<0.01**
Steps per day (per 1000 steps)	0.80	0.71	0.91	**<0.01**	0.81	0.71	0.93	**<0.01**
Hand grip, kg	0.98	0.96	1.00	0.12	0.98	0.96	0.99	**0.01**
30 s Sit-Stand (per repetition)	0.97	0.93	1.01	0.15	0.93	0.89	0.98	**<0.01**
Sit-reach (per cm)	1.02	0.99	1.04	0.26	1.00	0.98	1.03	0.90
Up and Go (per second)	1.08	1.00	1.18	0.06	1.16	1.08	1.24	**<0.01**
Everything an effort (1+ vs 0)[a]	1.04	0.64	1.72	0.86	1.00	0.61	1.63	0.99
Could not get going (1+ vs 0)[a]	1.79	1.09	2.93	**0.02**	1.41	0.85	2.34	0.19
Lost 10 lb (yes/no)	1.46	0.91	2.34	0.12	1.43	0.88	2.34	0.15

[a] Patients were asked 2 CES-D questions: how many days in the past week (0–7 d) (a) was everything you did an effort, and (b) could you not get going? Results are reported according to whether the patient answered that they had no versus one or more days per week where everything was an effort, or they could not get going.
Bold values indicate statistical significance.
BMI, body mass index; BNP, *N*-terminal pro-brain natriuretic peptide; CES-D, Center of Epidemiological Studies Depression Scale; CI, confidence interval; METS, metabolic equivalents.

TABLE 4.

Demographics, biochemical, and functional metrics stratified according to follow-up reason

	No follow-up	All follow-up	Routine follow-up	Nonroutine follow-up
N	**174**	**139**	**92**	**47**
Age, y[a]	60.5 (9.8)	62 (9.7)	62.4 (9.6)	61.1 (9.9)
Sex (male) %	95.5	95.7	95.7	97.9
Race (White) %	65.5	66.2	64.1	70.2
Diabetes %	57.2	64.7	55.4	83
Hypertension %	97.1%	96.4	95.7	97.9
BMI[a]	29.2 (4.2)	29.7 (4)	29 (3.9)	31 (4)
Troponin, ng/mL[b]	0.3 (0.1–0.7)	0.2 (0.1–0.8)	0.2 (0.1–0.5)	0.4 (0.1–1.1)
BNP, pg/mL[b]	1.5 (0.4–4.1)	1.2 (0.5–3)	0.9 (0.4–2.6)	1.7 (0.7–4.8)
METS[a]	5.8 (2.1)	5.7 (2.1)	6.3 (2.1)	4.6 (1.7)
Steps per day (per 1000)[b]	3.4 (2–5.4)	3.7 (2.3–5.2)	4.3 (2.7–5.8)	3 (1.4–4.4)
Hand grip, kg[a]	30.5 (10.5)	29.5 (10.1)	29.8 (10.2)	28.8 (9.9)
30 s Sit-Stand[a]	15.8 (6.2)	14.7 (6.2)	16 (6.1)	12.5 (5.7)
Sit-reach, cm[b]	0 (0–6)	0 (0–9)	0 (0–8)	0 (0–9)
Up and Go, s[b]	5.1 (4.1–6.3)	5.2 (4.4–6.5)	4.9 (4.3–5.7)	6.4 (5.2–7.8)
Everything an effort, d/wk, %	34.6	32.8	28.9	40.4
Could not get going, d/wk, %	34.6	32.8	28.9	40.4
Lost 10 lb (yes/no) %	35.3	26.5	27	25.5

[a] Mean (SD).
[b] Median (IQR: Q1–Q3).
BMI, body mass index; BNP, *N*-terminal probrain natriuretic peptide; IQR, interquartile range; METS, metabolic equivalents.

Multivariate Time-to-Event Modeling of Waiting List Removal for Death or Medical Delisting

Backward logistic regression model selection resulted in an optimal predictor set that included BNP (OR = 1.02 per 1000 pg/mL increase, 95% CI, 1.00-1.04, P = 0.02), pedometer activity (OR = 0.82 per 1000 steps/d increase, CI, 0.72-0.92, P < 0.01), and the CES-D question asking how many days per week the patient could

TABLE 5.

Associations between variables and need for nonroutine follow-up

		95% CI		
	Odds ratio	Lower	Upper	*P* value
Age, y	0.99	0.95	1.02	0.47
Sex (male)	1.02	0.18	5.82	0.98
Race (White)	1.32	0.62	2.79	0.47
Diabetes	3.92	1.68	9.13	**<0.01**
Hypertension	2.09	0.32	13.58	0.44
BMI	1.14	1.04	1.25	**0.01**
Troponin	1.63	0.91	2.91	0.10
BNP	1.05	1.01	1.09	**0.02**
METS	0.62	0.50	0.78	**<0.01**
Steps per day	0.78	0.65	0.93	**<0.01**
Hand grip	0.99	0.96	1.03	0.59
30 s Sit-Stand	0.89	0.82	0.98	**0.01**
Sit-reach	1.03	0.99	1.07	0.16
Up and Go	1.52	1.22	1.89	**<0.01**
Everything an effort	1.67	0.79	3.55	0.18
Could not get going	2.01	0.89	4.54	0.09
Lost 10 lb (yes/no)	0.93	0.43	1.99	0.85

Bold values indicate statistical significance.
BMI, body mass index; BNP, *N*-terminal probrain natriuretic peptide; CI, confidence interval; METS, metabolic equivalents.

TABLE 6.

Optimal predictor set from backward logistic regression modeling

Parameter	Odds ratio	95% CI lower	95%CI upper	*P* value
BNP (per 1000 pg/mL increase)	1.02	1.00	1.04	0.02
Pedometer ability (per 1000 steps/d)	0.82	0.72	0.92	<0.01
CES-D question[a]	1.72	1.03	2.87	0.04

[a] CES-D question: how many days in the past week (0–7 d) could you not get going? Results are reported according to whether the patient answered that they had no versus one or more days per week when they could not get going.
BNP, *N*-terminal pro-brain natriuretic peptide; CES-D, Center of Epidemiological Studies Depression Scale; CI, confidence interval.

TABLE 7.

Optimal predictor set from backward Cox proportional hazard modeling

Parameter	Hazard ratio	95% CI lower	95% CI upper	*P* value
BNP (per 1000 pg/mL increase)	1.03	1.02	1.04	<0.01
Treadmill ability (per METS point increase)	0.80	0.69	0.92	<0.01
Age (per year increase)	1.03	1.00	1.06	0.05

BNP, *N*-terminal probrain natriuretic peptide; CI, confidence interval; METS, metabolic equivalents.

not get going (OR = 1.72, CI, 1.03-2.87, $P = 0.04$) (Table 6).

Backward Cox proportional hazards model selection resulted in an optimal predictor set that included BNP (HR = 1.03 per 1000 pg/mL increase, 95% CI, 1.02-1.04, $P < 0.01$), treadmill ability (HR = 0.80 per METS point increase, 95% CI, 0.69-0.92, $P < 0.01$), and patient age (HR = 1.03 per year increase, 95% CI, 1.00-1.06, $P = 0.05$) (Table 7).

BNP and a measure of walking ability (pedometer ability and treadmill for logistic regression and Cox modeling, respectively) were consistent predictors in both models.

To illustrate the most significant predictor variables in the multivariate models, Kaplan-Meier plots were created. The most significant predictors in the respective models are shown in Figures 1 and 2. Figures show the effect of different ranges of BNP, pedometer ability, treadmill ability (METS), age, and the response to the CES-D question asking the number of days per week a patient could not get going. Continuous measures were broken into 3 approximately even strata.

DISCUSSION

In this retrospective study of waitlisted patients, we sought to identify factors among the demographic, functional, frailty, and biochemical tests that we routinely collect that correlate with waitlist removal for adverse outcomes both at the time of listing and as a function of the change in these metrics over time. Our current process attempts to re-evaluate listed patients every 1–2 y, which is resource intense. BNP, treadmill ability, and pedometer activity were important predictors of waitlist removal for death and medical problems both at baseline and as a function of changes in these metrics over time. These same factors were also significantly associated with nonroutine follow-up visits, which often occurred after a change in the patients' health status. Additionally, diabetes and the CES-D question asking how many days per week a patient could not get going were associated with poor waitlist outcomes when measured at the time of listing.

BNP was significantly associated with negative outcomes in this study and is known to be strongly associated with incident and prevalent cardiac and all-cause mortality among renal failure patients.[20–27] Troponin levels have also been linked with dialysis and transplant outcomes.[28–32] We have previously shown an association with BNP and troponin in kidney transplant evaluation outcomes, in which troponin was more predictive in multivariable modeling.[4] In the current study, only BNP was associated with waitlist removal on multivariate analysis. Change in BNP over time was a significant predictor of waitlist removal.

Mortality risk increases according to BNP levels, with the highest interquartile risk groups starting at BNP levels between 8847 and 12 297 ng/L and correlating with 20% 1-y and 68% 4-y all-cause mortality.[20,21,24,26] When reporting single cut points associated with poor outcomes among patients on dialysis, investigators have reported values ranging between 4079 and 9649 ng/l for intervals between 16 mo and 2 y.[20,22–25] Groups that have studied change in BNP among dialysis patients over time have also shown worse survival with rising levels.[20,26] Interestingly, Winkler et al[26] also showed improved outcomes associated with a decrease in BNP over time. Of note, when troponin and BNP were evaluated in the same study, BNP was more strongly correlated with the study endpoints.[24,25]

There has been a gradual maturation in the appreciation of the prognostic limitations of cardiac stress testing as part of transplant evaluation.[33] Cardiac testing, while perhaps important for risk stratification, may not lead to therapeutic interventions that enhance survival and has been shown to delay

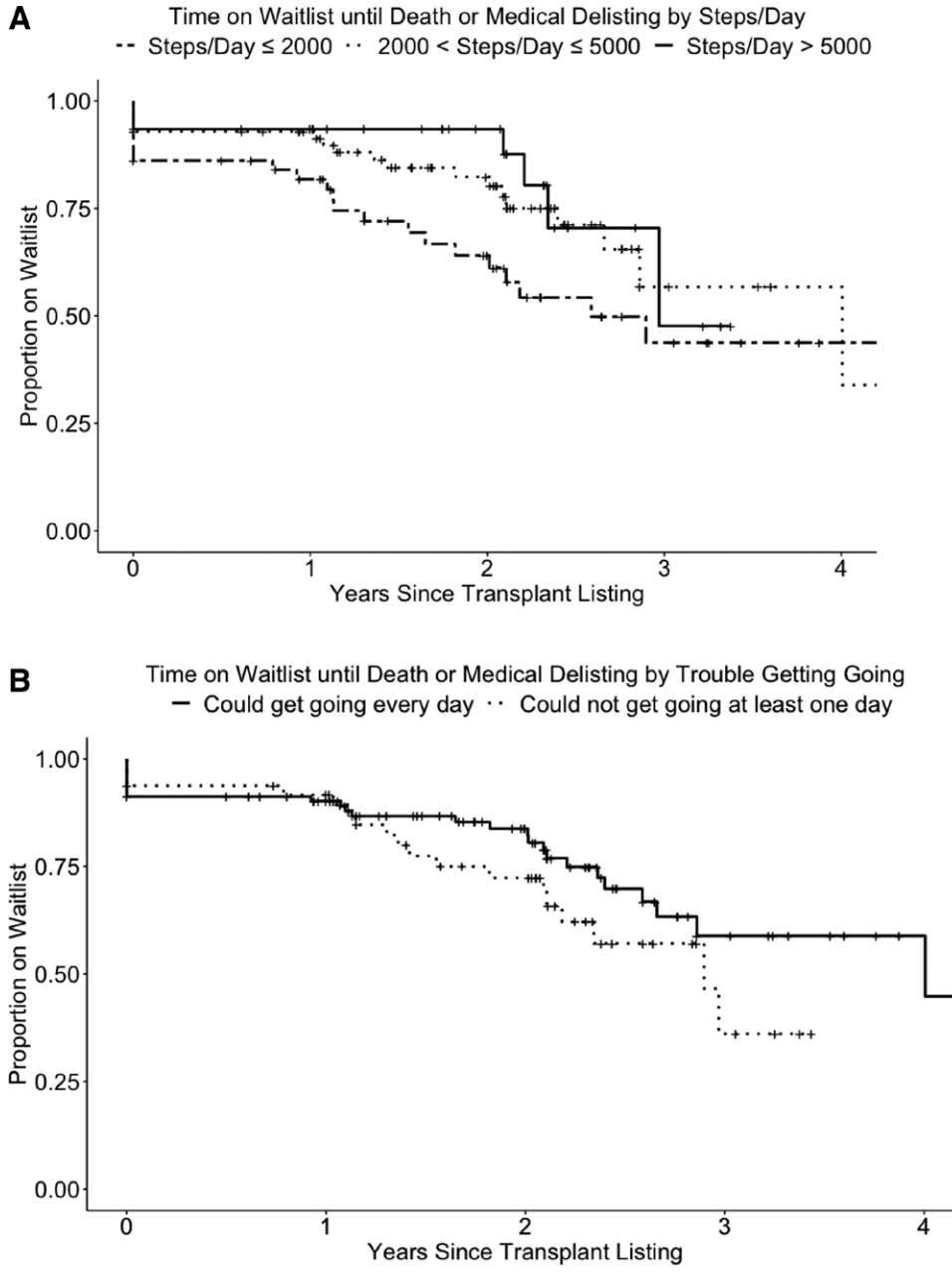

FIGURE 1. Kaplan-Meier plots showing the effect of differences in the top predictor variables from backward logistic regression modeling censored for outcome events (death or medical delist, hashmarks). The proportion of patients remaining on the waiting list is plotted against waiting time. Continuous measures were broken into 3 approximately even strata for comparison. A, Delisting is shown based on pedometer activity measured as steps per day (group 1: walking <2000 steps per day, group 2: between 2000 and 5000 steps per day, and group 3: >5000 steps per day). B, Delisting is plotted according to whether the patient answered the CES-D question that they could or could not get going 1 or more days per week. CES-D, Center of Epidemiological Studies Depression Scale.

the transplant evaluation process.[34] Simultaneously, there is growing appreciation for the value of functional or frailty assessments during candidate selection as important prognosticators of transplant and waitlist outcomes. Serially measuring BNP at the time of transplant re-evaluation may augment the cardiac re-evaluation process in transplant.

An evolving literature demonstrating a correlation between functional and frailty metrics and transplant outcomes has led to interest in incorporating these measures into waitlist management.[5,9,13,35–37] Following implementation of a new waitlist management strategy, Cheng et al[12] showed that physical performance was one of the main reasons for list removal. They concluded that their new system helped identify patients who were no longer suitable candidates. The same group has also shown that chair sit-stand testing and the 6-min walking test both correlated with waiting list survival and incorporation of both physical performance tests enhanced waitlist survival modeling. In our work, in addition to pedometer, treadmill, and Up and Go, change in chair sit-stand ability over time was also significant.

Walking speed is an individually important component of frailty measures and is associated with death on dialysis.[38–40] The American Society of Transplant Surgeons consensus statement on frailty recommends Fried testing for

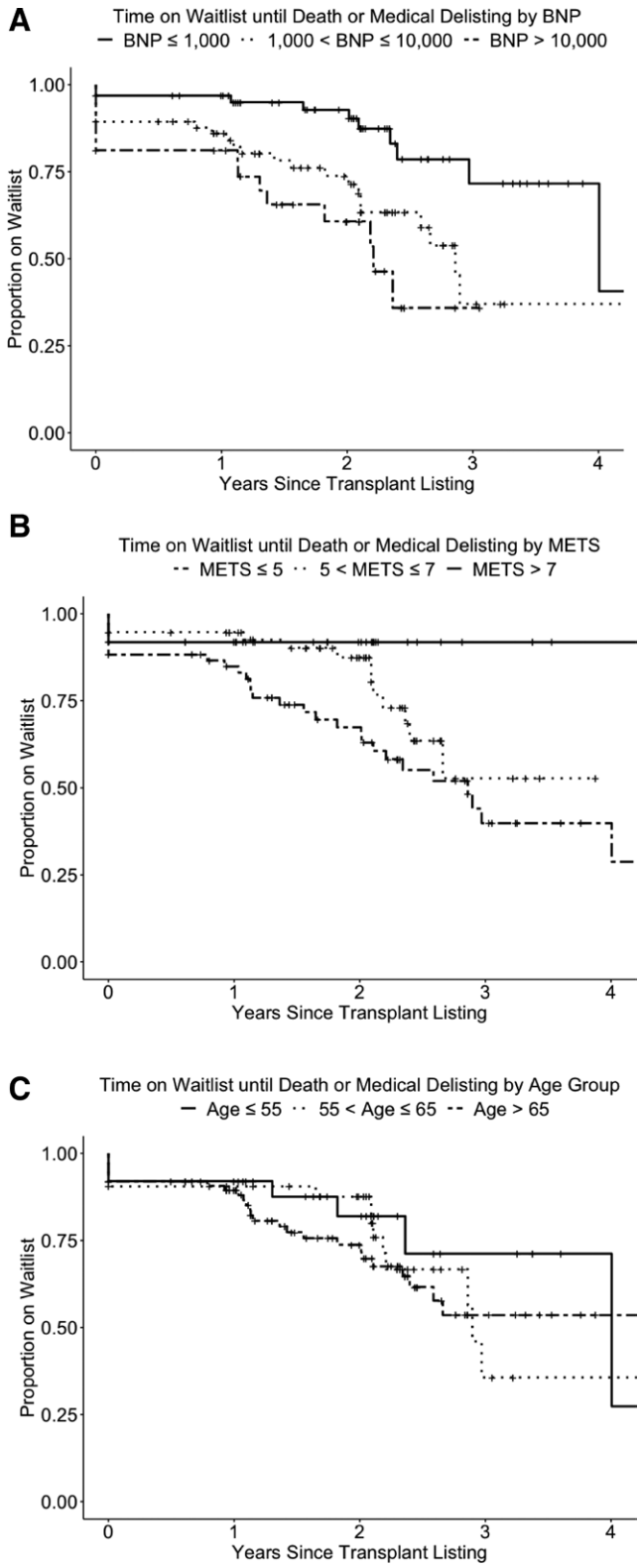

FIGURE 2. Kaplan-Meier plots showing the effect of differences in the top predictor variables from backward Cox proportional hazard modeling censored for outcome events. A, Patients grouped by level of BNP (group 1: BNP ≤1000, group 2: BNP between 1000 and 10 000, and group 3: BNP >10 000). B, Patients grouped according to treadmill ability (group 1: ≤5 METS, group 2: between 5 and 7 METS, group 3: >7 METS). C, Patients grouped by age (group 1: ≤55 y old, group 2: between 55 and 65 y old, and group 3: >65 y old). BNP, *N*-terminal pro-brain natriuretic peptide; METS, metabolic equivalents.

kidney transplant patients, perhaps because of portability and a broad experience in the kidney transplant literature.[41] Walking ability, as evaluated with the Up and Go test in Fried testing, was significantly associated with waitlist removal for death and medical reasons in our cohort. However, pedometer and treadmill testing remained significant on multivariate modeling. The odds of death or medical delist decreased by 18% per 1000 steps per day increase in pedometer activity and by 20% for every 1 MET increase in treadmill ability. Six-minute walk testing is readily available at many institutions; however, it may fail to stratify patients who are capable of high levels of stress and therefore fail to detect changes in this segment of patients over time.

Frailty has been associated with poor dialysis[42,43] and transplant outcomes, and despite literature showing time-dependent increases in frailty among dialysis patients,[44] objective frailty metrics have not been commonly included in prognostic tools of dialysis survival. A number of prognostic indices have been used or developed to predict dialysis outcome. Among the 32 studies included in the meta-analysis by Anderson et al evaluating factors predictive of the risk of death among patients starting dialysis, only 11 incorporated functional measures all of which were either simple observational metrics (such as transfer ability)[45,46] or evaluated, as with the 36-Item Short Form Health Survey, by questionnaire.[47] Although a number of the dialysis survival indices in this meta-analysis included laboratory information such as C-reactive protein, albumin, and lipid profiles, we are not aware of any that included BNP despite its being known to be associated with survival in renal failure patients and, in some reports, to correlate more strongly with mortality risk than C-reactive protein and albumin.[48,49] In our cohort, as BNP increased by 5000 pg/mL, there was an associated 11% increase in the odds of death or delisting for medical reasons.

Age and diabetes, as in this analysis, are also established risk factors for dialysis mortality[3] and are incorporated in many dialysis mortality prognostic indices.[47] During the years covered by this study, the average age of patients listed for transplant in the United States was <55 and 25%–26% of patients had renal failure attributed to diabetes,[3] compared with our patients who were older (59.9) and had a higher incidence of diabetes as the cause of renal failure (44%). This likely represents a general trend among the VA kidney transplant programs to list older patients with more comorbidities and social stressors than in the general US transplant population[50] and points to an increased need to do continued risk assessment among listed veterans.

Despite a well-known association between depression and dialysis mortality, depression is rarely included in dialysis survival models. Our results showed that the risk of death or delist for medical reasons was 72% higher for patients who could not get going 1 or more days per week. In the meta-analysis by Farrokhi et al,[51] looking at the association between depression and mortality on dialysis, the majority of studies included in the analysis found depression to be a significant risk factor even when measured against traditional demographic, laboratory, and clinical variables. For example, Miskulin et al[52] showed that depression was one of only a few comorbid conditions that predicted mortality on dialysis. In identifying an association between the CES-D

question and delisting, our results are consistent with prior work linking depression and dialysis mortality and suggest that depression is prognostically important in predicting waitlist removal.

This study is limited by bias inherent in single-center retrospective analyses. Also, because almost all the patients were male, the ability to extrapolate the results to populations of female transplant candidates may be limited. This study used a composite endpoint of mortality and delisting for medical reasons when the predominate reasons for waitlist removal skewed to cardiovascular and functional factors. Therefore, the risk factors identified may not be as applicable to other causes of delisting. As noted in the Materials and Methods section, a change from the Bruce to Naughton protocol was made after the first 38 patients, which could have introduced bias or inconsistency to the METS data portion of the study. A potential source of bias, particularly in the case of delisting for functional decline, is that team members could have been aware of the various study metrics. The general applicability of adding treadmill and pedometer testing to the evaluation process could be limited because these tests require special equipment and training.

In conclusion, this study showed that BNP, and several frailty and functional metrics are associated with kidney transplant waitlist removal. Factors that were consistent across models included measures of walking ability and BNP. In waitlisted candidates measuring these factors over time could be used to triage candidates' re-evaluation needs or be used as a basis for referral for prehabilitation. Additional prospective studies are needed to measure the potential impact of frailty and BNP surveillance on waitlist management.

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