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Metabolic syndrome definitions and components in predicting major adverse cardiovascular events after kidney transplantation

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Summary

Metabolic syndrome (MetS) associates with cardiovascular risk post-kidney transplantation, but its ambiguity impairs understanding of its diagnostic utility relative to components. We compared five MetS definitions and the predictive value of constituent components of significant definitions for major adverse cardiovascular events (MACE) in a cohort of 1182 kidney transplant recipients. MetS definitions were adjusted for noncomponent traditional Framingham risk factors and relevant transplant-related variables. Kaplan–Meier, logistic regression, and Cox proportional hazards analysis were utilized. There were 143 MACE over 7447 patient-years of follow-up. Only the World Health Organization (WHO) 1998 definition predicted MACE (25.3 vs 15.5 events/1000 patient-years, $P = 0.019$). Time-to-MACE was 5.5 ± 3.5 years with MetS and 6.8 ± 3.9 years without MetS ($P < 0.0001$). MetS was independent of pertinent MACE risk factors except age and previous cardiac disease. Among MetS components, dysglycemia provided greatest hazard ratio (HR) for MACE (1.814 [95% confidence interval 1.26–2.60]), increased successively by microalbuminuria (HR 1.946 [1.37–2.75]), dyslipidemia (3.284 [1.72–6.26]), hypertension (4.127 [2.16–7.86]), and central obesity (4.282 [2.09–8.76]). MetS did not affect graft survival. In summary, although the WHO 1998 definition provides greatest predictive value for post-transplant MACE, most of this is conferred by dysglycemia and is overshadowed by age and previous cardiac disease.

Introduction

The association of metabolic syndrome (MetS) with increased cardiovascular risk in the general population [1, 2] is extendable to kidney transplant recipients [3, 4], a population whose cardiovascular risk is already high [5]. However, the underlying pathophysiology behind this association in the post-transplant milieu requires extensive clarification [6]. Furthermore, ambiguity has resulted from the pragmatic adaptation of different MetS definitions [7–11], leading to further uncertainty to the value of assigning this diagnosis to kidney transplant recipients. The components of these MetS definitions are so variable that their relative contribution to post-transplant cardiovascular risk also remains undetermined. The purpose of this study therefore was to compare the value of five commonly used MetS definitions [7–11] and the components of the predictive definitions among them for long-term cardiovascular events in a cohort of kidney transplant recipients.

Patients and methods

St. Michael's Hospital is an urban university-affiliated tertiary care medical-surgical center that performs about 120

adult single-organ kidney transplants annually. Clinical data including cardiovascular outcomes have been collected prospectively since 2004 from an electronic hospital database, supplemented by patient interview and family physician contact where necessary to capture events occurring at other hospitals. Professional interpreters are used wherever necessary. In this study, we included all kidney transplant recipients with minimum 3 months post-transplant graft survival who received their allograft between January 1, 1998 and December 31, 2010 and were followed at our center, excluding those with type 1 diabetes. Demographic and cardiovascular event data on patients transplanted prior to July 1, 2004 were collected retrospectively to that date and prospectively thereafter, with follow-up to June 30, 2012. Research Ethics Board approval was obtained for the study (REB 10-204, 2010). The study fulfills criteria of the 2000 Declaration of Helsinki and the 2008 Declaration of Istanbul.

MetS at three months post-transplant was defined using five methods: the International Diabetes Federation (IDF) 2005 criteria [7], World Health Organization (WHO) 1998 criteria [8], US National Cholesterol Education Program Adult Treatment Panel III original 2001 [9] and updated 2004 [10] definitions, and the harmonized, or consensus 2009 definition [11] (see Appendix 1). Patients receiving medication for hypertriglyceridemia (e.g., statins and fibrates) and hypertension were classified as satisfying these components of the MetS definition when applicable and if not otherwise specified. Likewise, a diagnosis of diabetes was satisfied if end-stage renal disease had been attributed to diabetic nephropathy, or the patient received oral hypoglycemic therapy or insulin at the time. Pre-existing type 2 diabetes as well as glucose intolerance or new-onset diabetes after transplantation (NODAT) lasting to 3 months post-transplant were combined into a single dysglycemia variable. For this study, new-onset diabetes (NODAT) was defined based on Canadian Diabetes Association 2008 guidelines [12]. Microalbuminuria was defined as morning urine albumin-to-creatinine ratio $\geq$2.0 mg/mmol for men and $\geq$2.8 mg/mmol for women in keeping with Canadian guidelines [12]. HDL cholesterol measurements were obtained from a fasting lipid profile. Along with body mass index (BMI), waist and hip circumference measurements are obtained in the clinic by 3 months post-transplant and at least annually thereafter.

We defined major adverse cardiovascular events (MACE) as one or more of the following: hospital diagnosis of acute coronary syndrome (including unstable angina, abnormal exercise or pharmacologic stress test), coronary angiography demonstrating significant stenosis in at least one major epicardial artery, percutaneous coronary intervention (angioplasty with or without stenting), coronary artery bypass surgery, sudden death because of a cardiac event, congestive heart failure (CHF) requiring hospitalization, and stroke. Stable angina was excluded. All events were verified independently by a review performed by at least two investigators. Other demographic data that were collected included all relevant pre-, peri-, and post-transplant variables, including acute rejection or the use of intravenous methylprednisolone therapy any time after initial hospital discharge, and delayed graft function, defined as the need for dialysis in the first post-transplant week. Graft loss was defined as a permanent return to dialysis or repeat transplantation, and patient death was ascertained from hospital records. The estimated GFR (eGFR) was calculated from the abbreviated MDRD equation [13]. Previous cardiac disease was defined similar to post-transplant events with the important exception being that all transplant candidates necessarily undergo pre-transplant screening through cardiac stress testing, unlike post-transplant where testing is performed by indication only.

As cardiovascular events may be divided into those occurring early, where the major contributing risk factors relate most to pre-existing disease burden and the operative procedure itself, and those occurring later, where more traditional risk factors predominate, proportionality of hazards was assumed starting at 3 months post-transplant. The primary analysis therefore included all events occurring beyond 3 months post-transplant, with any MACE prior to 3 months counted as previous cardiac disease. The value or status for all other traditional Framingham variables [14] and relevant laboratory or clinical assessment at 3 months post-transplant was utilized subsequently in the analysis. A secondary analysis of graft survival after 3 months was also performed.

Kaplan–Meier survival analysis for MACE was performed starting at 3 months post-transplant, using each MetS definition separately, with survival compared by the log-rank test. Patients were censored if lost to follow-up for 1 year. A priori univariate analysis for MetS definitions showing predictive value for MACE was performed using ANOVA or chi-square testing as appropriate. Logistic regression analysis was employed to assess the impact of such definitions on MACE adjusting for traditional Framingham risk factors not contained within the concerned MetS definition and relevant allograft-related risk factors, with backwards elimination of variables with $P > 0.20$ successively removed until a final stable model was attained. A Cox proportional hazards regression model was developed to estimate hazard ratios first computed for the mandatory components of those definitions, if any, in isolation followed by the successive addition of other components in all possible combinations. All data are reported as mean $\pm$ SD unless otherwise stated. A P value of <0.05 was taken to imply statistical significance. SAS version 9.2® (Cary, NC, USA) was the statistical software package used for the analysis.

Results

After excluding patients with type 1 diabetes ($N = 30$) and graft failure ($N = 29$) or patient death ($N = 18$) within the first three months post-transplant, there were 1182 patients available for analysis. Age at transplant for this entire cohort was 49.3 ± 13 years (range 17–78), and 744 (63%) were male; ethnicity was 60% Caucasian, 8% African–Canadian, 14% East Asian and 16% South Asian; 48% were living donor and 15% were smokers at the time of transplant. Cause of ESRD was diabetes in 13%, hypertension in 12%, glomerulonephritis in 42%, and polycystic kidney disease in 13%. Of the cohort, 62% were on hemodialysis and 24% were on peritoneal dialysis prior to the transplant with mean dialysis duration 4.3 ± 3.5 years, while 14% received a pre-emptive living donor transplant. Overall delayed graft function rate was 11% and acute rejection rate 13% by 3 months post-transplant. There were 220 patients (18.6%) with a documented prior history of cardiac disease. The incidence of NODAT at 3 months was 25%. There were 61 patients with MACE in the first three months post-transplant. Total follow-up was 7447 patient-years.

Prevalence of MetS at 3 months post-transplant ranged from 36% by the harmonized (consensus) 2009 definition to 50% by the AHA/NHLBI 2004 definition (Table 1). Post-3 months, there were a total of 143 MACE during long-term follow-up (Table 1). Kaplan–Meier survival curves for the IDF, WHO, NCEP, updated NCEP, and harmonized (consensus) definitions for the MetS are provided in Fig. 1(a–e). Of all these definitions, only the WHO definition was significantly predictive of post-transplant MACE (Table 1). Of these, 84 (59%) were acute myocardial infarctions, 13 (9%) sudden cardiac death, 5 (3.5%) stroke, 16 (11%) hospitalization for CHF, and 25 (17.5%) were coronary revascularization procedures (angioplasty or bypass grafting). Based on this result, only the WHO definition was subjected to further analysis. There were no differences in type of MACE between those with and without MetS. Time-to-MACE was 5.5 ± 3.5 years in those with MetS versus 6.8 ± 3.9 years in those without MetS ($P < 0.0001$). Table 2 provides a comparison of patient features classified on the basis of their fulfillment of the WHO definition for MetS.

The results of the univariate analysis and adjusted models for MACE by logistic regression analysis are shown in Table 3. Multivariate adjustment of MetS presence by Framingham risk factors not contained in the WHO definition including sex, smoking history, or LDL cholesterol, as well as allograft-related factors including eGFR and type of calcineurin-inhibitor did not affect the statistical significance of MetS, but adjustment by either age (a Framingham risk factor) or history of previous cardiac disease rendered MetS nonsignificant. Table 4 demonstrates the hazard ratio of dysglycemia (insulin resistance), the mandatory component of the WHO definition, compared to normoglycemia, followed by the addition of hypertension, dyslipidemia, central obesity, and microalbuminuria in succession. This illustrates that most of the cardiovascular hazard conferred by MetS was attributable to dysglycemia, although the addition of other components in the WHO definition for MetS increased this hazard further. Among these, microalbuminuria provided the greatest added risk to dysglycemia alone, followed by dyslipidemia (high triglycerides, low HDL, or both) and then hypertension (Table 4). There was no difference to the result whether BMI or waist/hip measurements were used as the measure of central obesity in any of the relevant definitions by secondary analysis. There was no impact of MetS on long-term death-censored graft survival (Fig. 2).

Table 1. Predictive value of each metabolic syndrome definition for predicting post-transplant major adverse cardiovascular events (MACE) in 1182 patients by Kaplan–Meier analysis.

MetS Definition	Value	Patients (*N*) (%)	Years of follow-up (*N*)	MACE (*N*)	MACE Rate/ 1000 years at risk	*P*-Value (log-rank test)
IDF 2005	Absent	638 (54)	4166	76	18.2	0.704
	Present	544 (46)	3281	67	20.4	
WHO 1998	Absent	677 (58)	4642	72	15.5	0.019
	Present	505 (42)	2805	71	25.3	
NCEP-ATP III 2001	Absent	617 (53)	4060	68	16.7	0.191
	Present	565 (47)	3387	75	22.1	
AHA/NHLBI 2004	Absent	581 (49)	3844	63	16.4	0.150
	Present	601 (51)	3603	80	22.2	
Harmonized (Consensus) 2009	Absent	757 (64)	4915	83	16.9	0.081
	Present	425 (36)	2532	60	23.7	

IDF, International Diabetes Federation; WHO, World Health Organization; NCEP-ATP, National Cholesterol Education Program Adult Treatment Panel III; AHA/NHLBI, American Heart Association/National Heart, Lung, and Blood Institute; MACE, major adverse cardiovascular event; MetS, metabolic syndrome.

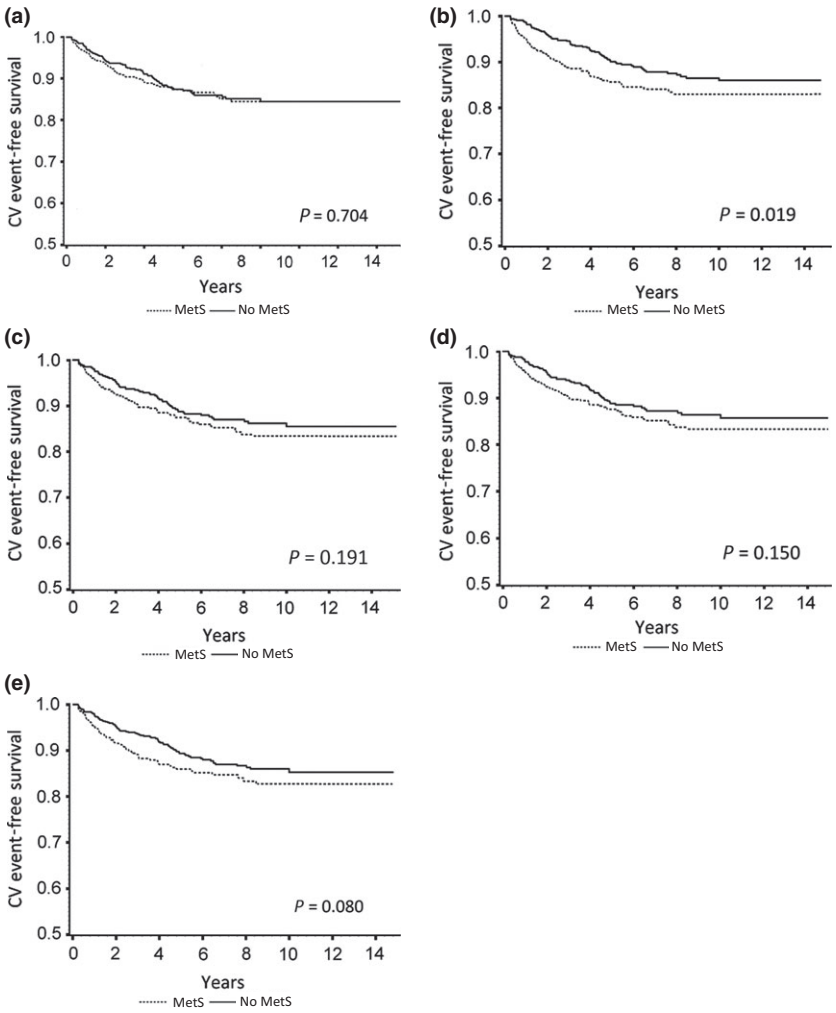

Figure 1 (a–e): Kaplan–Meier survival curves for major adverse cardiovascular events (MACE) using five different metabolic syndrome definitions (a) International Diabetes Federation 2005 ($P = 0.703$), (b) World Health Organization 1998 ($P = 0.019$), (c) National Cholesterol Education Program Adult Treatment Panel III (NCEP:ATPIII) 2001 ($P = 0.191$), (d) American Heart Association/National Heart, Lung, and Blood Institute(AHA/NHLBI) 2004 ($P = 0.150$), and (e) Harmonized (Consensus) Definition incorporating IDF and AHA/NHLBI definitions 2009 ($P = 0.080$).

Discussion

In this study, we have demonstrated that among the various MetS definitions, the 1998 WHO definition which includes dysglycemia (insulin resistance) as its primary component plus any two among hypertension, dyslipidemia, central obesity, and microalbuminuria provides the best predictive value for the development of significant long-term cardiovascular disease in kidney transplant recipients. This effect is independent of many other cardiovascular and transplant-related risk factors, but is overshadowed by increasing age and a prior history of cardiovascular disease. Most of this risk from MetS is conferred by dysglycemia, but the addition of other components adds incrementally to this risk. Conversely, the other widely used definitions for MetS did not significantly predict cardiovascular events. There was no significant impact of MetS on graft survival. Therefore, MetS as a predictor of cardiovascular disease is peripheral at best.

The two largest studies to assess the relationship between MetS and cardiovascular outcomes in kidney transplant recipients are the Patient Outcomes in Renal Transplantation (PORT) [4] and Assessment of Lescol in Renal Transplantation (ALERT) [15] studies. In a substudy of PORT, the investigators demonstrated an association between MetS and coronary heart disease (hazard ratio 2.03, 95% CI 1.16–3.52, $P = 0.013$) in 2253 kidney transplant recipients [4]. In ALERT, 1706 nondiabetic kidney transplant recipients

Table 2. Comparison of patients with and without the metabolic syndrome based on the WHO 1998 definition.

Parameter	WHO MetS Present (*N* = 505)	WHO MetS Absent (*N* = 677)	*P* value
Pre-Transplant Variables			
Age at transplant (years)	53.2 ± 11 (18–77)	46.4 ± 13 (16–78)	<0.0001
Sex (M/F)(N/%)	340 (67)/165 (33)	404 (60)/273 (40)	0.017
Ethnicity			
Caucasian	271 (54)	427 (64)	0.001
African-Canadian	45 (9)	52 (8)	0.446
East Asian	69 (14)	95 (14)	0.855
South Asian	101 (20)	84 (13)	0.0004
Others	12 (3)	8 (1)	0.073
Donor Source (living/deceased) (N/%)	267 (54)/233 (46)	330 (49)/337 (51)	0.184
End-Stage Renal Disease Etiology (N/%)			
Diabetes	104 (21)	44 (7)	<0.0001
Hypertension	65 (13)	70 (10)	0.175
Glomerulonephritis	189 (38)	301 (44)	0.015
Polycystic Kidney Disease	50 (10)	101 (15)	0.010
Others	95 (19)	159 (24)	0.204
Number of transplants (1/2/3)	481/22/2	630/46/1	0.146
Smoking	71 (14)	110 (16)	0.301
Pre-Transplant Dialysis (HD/PD/None) (N/%)	255 (63)/100 (25)/48 (12)	282 (62)/107 (23)/70 (15)	0.355
Dialysis Duration (if applicable) (years)	4.4 ± 2.8	4.3 ± 3.9	0.78
Previous Cardiac Disease (N/%)	108 (21)/397 (79)	112 (16)/565 (84)	0.034
Post-Transplant Variables			
Delayed Graft Function (N/%)	52 (10)	70 (10)	0.981
Acute Rejection (N/%)	58 (11)	89 (13)	0.398
Serum Creatinine (at 3 months) (μmol/l)	132 ± 73	129 ± 70	0.514
eGFR (ml/min/1.73 m^2)	56 ± 21	58 ± 21	0.180
Immunosuppressive Medication (at 3 months) (N/%)			
Tacrolimus	380 (75)	465 (68)	0.013
Cyclosporine	77 (15)	132 (19)	0.057
MPA or MMF	420 (83)	525 (77)	0.199
Azathioprine	13 (2)	9 (1)	0.118
Prednisone	418 (83)	564 (83)	0.784
Cardio-Protective Medication (N/%)			
ASA	114 (23)	74 (11)	<0.0001
ACE-I or ARB	174 (36)	199 (38)	0.808
Beta Blockers	207 (43)	148 (29)	<0.0001
Statins	240 (47)	187 (27)	<0.0001
MetS and Related Components			
Diabetes, IGT, or IFG (dysglycemia)	220 (44)	80 (12)	<0.0001
Systolic BP	131 ± 16	126 ± 15	<0.0001
Diastolic BP	78 ± 10	78 ± 9	0.376
Weight (kg)	76 ± 16	71 ± 15	<0.0001
BMI (kg/m^2)	26 ± 5	25 ± 4	<0.0001
Waist Circumference (cm)	99 ± 15	91 ± 14	<0.0001
Hip Circumference (cm)	104 ± 14	101 ± 13	<0.0001
Waist-Hip Ratio	0.96 ± 0.07	0.91 ± 0.08	<0.0001
Total Cholesterol (fasting) (mmol/l)	4.70 ± 1.1	4.78 ± 1.2	0.272
HDL Cholesterol (fasting) (mmol/l)	1.22 ± 0.4	1.37 ± 0.4	<0.0001
LDL Cholesterol (fasting) (mmol/l)	2.63 ± 0.9	2.66 ± 0.9	0.654
Triglycerides (fasting) (mmol/l)	1.90 ± 0.9	1.68 ± 0.87	<0.0001
Urine albumin-to-creatinine ratio (μg/μmol)	13 ± 31	14 ± 67	0.642
Uric Acid (μmol/l)	393 ± 115	386 ± 101	0.632
C-reactive protein (mg/l)	7.7 ± 18	7.3 ± 19	0.763

ACE-I, Angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ASA, acetylsalicylic acid; BMI, body mass index; HDL, high density lipoprotein; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; LDL, low density lipoprotein; MPA, mycophenolic acid; MMF, mycophenolate mofetil; MetS, metabolic syndrome.

Table 3. Analysis of Risk Factors for major adverse cardiovascular events (MACE) by logistic regression analysis.

Univariate Analysis			Adjusted model without Age and Previous Cardiac Disease		Adjusted Model with Age		Adjusted Model with Previous Cardiac Disease	
Variable	Chi-square	*P*-value	Chi-square	*P*-value	Chi-square	*P*-value	Chi-square	*P*-value
MetS by WHO definition	3.171	0.074	5.429	0.019	0.445	0.504	3.187	0.074
Age (per 10 years)	53.278	<0.0001			33.768	<0.0001		
Gender (male vs female)	13.150	0.0003	4.424	0.035	6.608	0.010	5.014	0.025
Smoking	17.132	<0.0001	2.027	0.154	1.966	0.160	1.165	0.280
Donor source (deceased vs live)	4.507	0.033	0.075	0.783	0.027	0.868	1.426	0.232
LDL cholesterol (per mmol/l)	0.0007	0.978	4.441	0.035	0.806	0.369	0.310	0.577
Previous cardiac disease	74.368	<0.0001					31.908	<0.0001
eGFR (per 10 ml/min/1.73 m^2)	0.457	0.498	0.036	0.849	0.010	0.917	0.082	0.774
Tacrolimus (vs cyclosporine)	0.144	0.704	0.031	0.858	0.149	0.698	0.194	0.659

LDL, low density lipoprotein; MACE, major adverse cardiovascular events; MetS, metabolic syndrome; WHO, World Health Organization.

were followed for 7–8 years. MetS was associated with a 16% incidence of MACE, compared to 11% in those without MACE ($P < 0.001$) [15]. An association with allograft failure was detected in PORT but not ALERT. Both studies utilized only the NCEP-ATP III definition of MetS. When compared to PORT and ALERT, this study is a unique contribution in several respects. The kidney transplant recipient population in Toronto, Canada, is multiethnic, and for the first time to our knowledge, ethnicity-specific criteria were employed when defining MetS. As expected, South Asians had a higher prevalence of MetS, and as we have shown previously [16], are a high-risk group for post-transplant MACE independent of age and previous cardiac disease. Granular information was available for waist and hip circumference measurements as well as microalbuminuria. By these virtues, this study also provides for the first time a direct comparison of prevalence as well as predictive value for five different MetS definitions in the transplant population and details the contribution of each component alone and in combination with other components, unlike in previous studies [4,15]. These data can be used to counsel individual patients of their cardiovascular risk and provides a framework for further study of MetS components in other transplanted populations.

The current study has some limitations. This was a single-center study, and the definition of MACE was broad, although 122 (85%) of events included the more traditional MACE constituents of acute coronary syndrome, coronary revascularization, and sudden cardiac death. The absolute number of MACE recorded was small, leading to reduced statistical power to detect associations. The mere existence of several MetS definitions suggests the high degree of relevance of its unclear understanding, and this may be aggravated by the definition used for MACE in this study. The study also does not offer a pathophysiological explanation for the relationship between MetS and MACE. However, insulin resistance post-transplant is clearly important as a cardiovascular risk factor in addition to powerful predictors such as advanced age and previous cardiac disease, and requires further clarification.

Attempts to explain cardiovascular disease using traditional risk factors in kidney transplant recipients have met with only partial success [17,18]. It is tempting to speculate that gaps between expected and observed cardiovascular event rates could at least partly be explained by MetS. These data however should not be taken to construe that there is no value to using definitions besides the WHO version. On the other hand, some of the other definitions are more practical to utilize when clinic time and resources are limited. The NCEP-ATP III definition is especially used in transplant-related studies [3,4,15]. Variation in prevalence estimates for MetS likely resulted from diversity in MetS's inclusion criteria. This study demonstrates that the WHO definition's distinctive parameters (such as microalbuminuria) and emphasis on dysglycemia as a mandatory component resulted in better performance and so these are appropriate for transplant cohorts. Diabetes in particular has a major impact on post-transplant cardiac events [19] and in this analysis did not require combination with any other component to be significant. Adjustment was made for eGFR as poor renal function is a cardiovascular risk factor, and calcineurin-inhibitor type because of the difference seen in MetS vs non-MetS. We focused on analyzing the WHO definition further as it alone was statistically significant as its own entity, but analysis of the other four definitions may yield similar results. The other four definitions may have "failed" to predict MACE in our study because they do not emphasize dysglycemia. Conversely, the WHO definition cannot

Table 4. Cumulative effect of WHO 1998 metabolic syndrome components for major adverse cardiovascular events (MACE) prediction by Cox regression analysis.

Component	Present (*N*)	Absent (*N*)	Parameter Estimate	Standard Error	Chi-Square	*P* value for Model	Hazard Ratio*	95% CI
One Component								
Dysglycemia	703	479	0.596	0.185	10.361	0.001	1.814	1.262–2.607
Hypertension	892	290	0.088	0.195	0.205	0.650	1.092	0.746–1.600
Dyslipidemia	134	1048	0.112	0.252	0.196	0.658	1.118	0.682–1.832
Central Obesity	781	401	0.217	0.171	1.614	0.204	0.805	0.576–1.125
Microalbuminuria	431	751	0.294	0.171	2.946	0.086	1.342	0.959–1.877
Two Components								
Dysglycemia + Hypertension	570	612	0.394	0.169	5.467	0.019	1.483	1.066–2.064
Dysglycemia + Dyslipidemia	89	1093	0.491	0.265	3.418	0.065	1.633	0.971–2.748
Dysglycemia + Central Obesity	482	700	0.251	0.168	2.220	0.136	1.285	0.924–1.788
Dysglycemia + Microalbuminuria	282	900	0.666	0.178	13.994	0.0002	1.946	1.373–2.758
Three Components								
Dysglycemia + Hypertension + Dyslipidemia	68	1114	0.650	0.281	5.328	0.021	1.915	1.103–3.325
Dysglycemia + Hypertension + Central Obesity	402	780	0.280	0.173	2.630	0.105	1.324	0.943–1.857
Dysglycemia + Hypertension + Microalbuminuria	242	940	0.706	0.185	14.635	0.0001	2.026	1.411–2.910
Dysglycemia + Dyslipidemia + Central Obesity	71	1111	0.522	0.291	3.221	0.073	1.686	0.953–2.982
Dysglycemia + Dyslipidemia + Microalbuminuria	34	1148	1.189	0.329	13.054	0.0003	3.284	1.723–6.261
Dysglycemia + Central Obesity + Microalbuminuria	212	970	0.672	0.194	12.005	0.0005	1.959	1.339–2.866
Four Components								
Dysglycemia + Hypertension + Dyslipidemia + Central Obesity	52	1130	0.689	0.314	4.818	0.028	1.992	1.077–3.685
Dysglycemia + Hypertension + Dyslipidemia + Microalbuminuria	28	1154	1.418	0.329	18.528	<0.0001	4.127	2.164–7.869
Dysglycemia + Hypertension + Central Obesity + Microalbuminuria	187	995	0.697	0.202	11.894	0.0001	2.008	1.351–2.985
Dysglycemia + Dyslipidemia + Central Obesity + Microalbuminuria	28	1154	1.166	0.365	10.202	0.0001	3.208	1.569–6.560
Five Components								
Dysglycemia + Hypertension + Dyslipidemia + Central Obesity + Microalbuminuria	22	1160	1.454	0.365	15.868	<0.0001	4.282	2.093–8.759

*Reference group is no dysglycemia (insulin resistance). Combinations providing the greatest step-increment to hazard ratios are highlighted. MACE, major adverse cardiovascular events; WHO, World Health Organization.

be used to predict NODAT because dysglycemia is a mandatory component.

Importantly, microalbuminuria provided the greatest incremental increase in hazard over dysglycemia alone. Early low-grade proteinuria and microalbuminuria predict the development of cardiovascular events [20] and so could be a useful tool independent of MetS. The greater impact seen with microalbuminuria compared to hypertension is unusual, although it is important to note that both were nonsignificant risk factors in isolation. This does not downplay the importance of good blood pressure control in kidney transplant recipients. As more patients had hypertension than microalbuminuria, there may have been less discriminatory power for the former as a variable. Microalbuminuria may also have a greater impact than hypertension on cardiovascular risk in those with dysglycemia, and therapies common to both such as renin-angiotensin system blockers may have a stronger differential effect on hypertension than on microalbuminuria. In this instance, microalbuminuria may either be a marker of endothelial dysfunction or poor graft function, but in either case, it

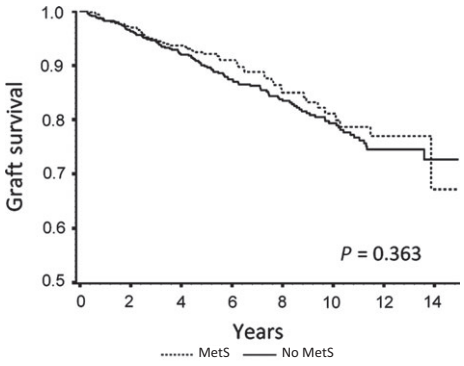

Figure 2 Kaplan–Meier death-censored graft survival by the World Health Organization 1998 definition ($P = 0.363$).

portends poorly for cardiovascular health when combined with dysglycemia. The more widespread prescription of cardioprotective medication in kidney transplant recipients may modify the relationship between MetS or its components and cardiovascular disease, making such associations more difficult to demonstrate in the future. Statins in particular may be beneficial as shown from ALERT study data (15), and along with other cardioprotective medications, were prescribed more frequently in our population for those with MetS. Nonetheless, these data confirm that more aggressive intervention be targeted to those with dysglycemia or microalbuminuria, than for instance, central obesity or an elevated CRP, although we were not able to discriminate between pre-transplant obesity and post-transplant weight gain. The poor performance of the IDF definition likely reflects its emphasis on central obesity. This study should be taken to highlight a hierarchy of risk factors with dysglycemia at the top, rather than emphasizing the actual hazard ratios as the latter will invariably differ by population being studied and can be therefore affected by other population-specific covariates. As MetS prevalence is relatively stable across time [4], attention is needed to these risk factors at all post-transplant life stages. A larger research goal would be to combine data across cohorts to study transplant-specific contributions and cut-offs for each MetS criterion.

There was no association between MetS and graft survival, unlike in some other reports [4]. This may have been because of a smaller sample size (about 52% of the PORT study [4]) but also intrinsic population characteristic (e.g., ethnic) or era differences. Graft survival is of course impacted by a multitude of distinct risk factors that are not necessarily related to cardiovascular disease and none of which differed by MetS presence. Immunosuppressive medication profiles including corticosteroid use, and early renal function, were no different between MetS and non-MetS groups. Long-term documented cardiovascular event rates themselves were overall quite low but consistent with other studies, in the order of 15–25 events per 1000 patient-years at risk. Each known cardiovascular risk factor should be managed individually [21] with the understanding that different MetS definitions may be associated with different pathophysiological markers [22]. Although quite expectedly age and previous cardiac disease overshadow MetS as a MACE risk factor, the greater predictive utility demonstrated by one MetS definition containing more inclusive information plus the additive value of its components suggests that there is utility to collecting more granular data as part of the post-transplant assessment, and may help guide more intensive intervention to particular patients based on their risk factor profile.

Authorship

Dr. Prasad: designed the study, analyzed the data, wrote and revised the manuscript; and directed overall project. Mr. Huang: analyzed the data. Drs. Rapi, Al-Lawati, Silver, and Ms. Nash: collected data and reviewed the critical content of manuscript. Dr. Zaltzman: reviewed the critical content of manuscript.

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Appendix 1 Criteria in definitions of the metabolic syndrome

Definition and its Criteria	Values
International Diabetes Federation (IDF) 2005	
Central obesity based on ethnicity	Waist circumference for Europeans >94 cm in men and 80 cm in women; South Asians, Chinese, and Japanese >90 cm in men and >80 cm in women; ethnic South and Central Americans use South Asian data; for sub-Saharan Africans and Eastern Mediterranean and Middle East (Arab) populations use European data. Can be assumed if BMI>30 kg/m^2
Plus two of the following	
Triglycerides	≥150 mg/dl (1.7 mmol/l)
HDL cholesterol	<40 mg/dl (1.03 mmol/l) in men and < 50 mg/dl (1.29 mmol/l) in women
Blood pressure	≥130 mmHg systolic; ≥85 mmHg diastolic; treatment of previously diagnosed hypertension
Fasting glucose	≥100 mg/dl (5.6 mmol/l), in which case oral glucose tolerance test is recommended
World Health Organization (WHO) 1998	
Insulin resistance	Type 2 diabetes mellitus or impaired fasting glucose (>100 mg/dl/5.6 mmol/l) or impaired glucose tolerance
Plus two of the following	
Abdominal obesity	Waist-to-hip ratio >0.9 in men or >0.85 in women or BMI >30 kg/m^2
Triglycerides and/or HDL cholesterol	>150 mg/dl (1.7 mmol/l) and/or <35 mg/dl (0.9 mmol/l) in men and <39 mg/dl (1.0 mmol/l) in women respectively
Blood pressure	≥140 mmHg systolic; ≥90 mmHg diastolic
Microalbuminuria	Urine albumin ≥20 μg/min or albumin-to-creatinine ratio ≥ 30 mg/g
National Cholesterol Education Program Adult Treatment Panel III (NCEP:ATPIII) 2001	
Any three or more of the following	

Appendix 1 (continued)

Definition and its Criteria	Values
Waist circumference	>102 cm in men and >88 cm in women
Triglycerides	≥150 mg/dl (1.7 mmol/l)
HDL cholesterol	<40 mg/dl (1.03 mmol/l) in men and <50 mg/dl (1.29 mmol/l) in women
Blood pressure	≥130 mmHg systolic; ≥85 mmHg diastolic
Fasting glucose	≥110 mg/dl (6.1 mmol/l) (≥100 mg/dl [5.6 mmol/l] since 2003)
American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) 2004	
Any three of the following:	
Waist circumference	>102 cm in men and >88 cm in women
Triglycerides	≥150 mg/dl (1.7 mmol/l)
HDL cholesterol	<40 mg/dl (1.03 mmol/l) in men and <50 mg/dl (1.29 mmol/l) in women
Blood pressure	≥130 mmHg systolic; ≥85 mmHg diastolic
Fasting glucose	≥100 mg/dl (5.6 mmol/l)
Harmonized (Consensus) Definition incorporating IDF and AHA/NHLBI definitions 2009	
Any three of the following	
Waist circumference	According to population and country-specific definitions
Triglycerides	≥150 mg/dl (1.7 mmol/l)
HDL cholesterol	<40 mg/dl (1.03 mmol/l) in men and <50 mg/dl (1.29 mmol/l) in women
Blood pressure	≥130 mmHg systolic; ≥85 mmHg diastolic
Fasting glucose	≥100 mg/dl (5.6 mmol/l) or use of medication

Appendix 2 Number of at-risk patients for Figures 1 and 2

	Years Post-Transplant									
	1	2	3	4	5	6	7	8	9	10
Figure 1a										
MetS	521	471	399	345	302	242	195	154	122	95
No MetS	605	547	487	432	375	322	266	221	187	150
Figure 1b										
MetS	474	423	347	300	259	209	156	114	88	65
No MetS	652	595	539	477	418	355	305	261	221	180
Figure 1c										
MetS	535	483	411	363	324	266	200	156	120	91
No MetS	591	535	475	414	353	298	261	219	189	154
Figure 1d										
MetS	569	514	438	384	343	281	213	165	129	99
No MetS	557	504	448	393	334	283	248	210	180	146
Figure 1e										
MetS	397	358	307	269	246	199	147	114	92	71
No MetS	729	660	579	508	431	365	314	261	217	174
Figure 2										
MetS	495	456	373	323	275	224	164	120	91	67
No MetS	664	615	558	494	437	375	330	279	238	196

