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Canonical Correlation Analysis of Risk Factors and Clinical Outcomes in Cardiac Surgery

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Assessment of the association between risk factors and outcomes in cardiac surgery is a complex problem. The aim of this study was to explore the relationship between possible risk factors and several clinical outcomes in cardiac surgery by using canonical correlation analysis (CCA). This retrospective study of 2605 consecutive adult patients who underwent cardiac surgery, evaluated 74 potential risk factors and up to 12 outcomes by canonical correlation analysis. For three serious outcomes, sternal wound complications/mediastinitis, cerebral complications, and perioperative myocardial infarctions, CCA was preceded by univariate analyses and backward stepwise multivariate logistic regression analyses. The CCA suggests that the major risk factors for complications in these models are intraoperative and postoperative risk factors. The power of risk prediction models developed with multivariate regression analysis can be enhanced by application of canonical correlation analysis, thereby offering new ways of analyzing and interpreting sets of potential risk factors in relation to sets of clinical outcomes.

KEY WORDS: adverse outcomes; canonical correlation analysis; cardiac surgery; multivariate logistic regression analysis; postoperative complications; risk factors.

INTRODUCTION

Measurements of clinical outcomes are needed for evaluation of patient benefits and analysis of the best use of health care resources. Several methods of quantifying risk and assessing outcome in cardiac surgery have been developed in the last few decades.[1–6] In Sweden, the Cleveland Clinic preoperative risk model (Higgins score)[2] and Parsonnet's risk stratification system from New Jersey,[3] two of the most well-known severity-adjusted models, are used. These two systems differ, as the Higgins score predicts both morbidity and mortality but has only

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been developed for coronary artery bypass surgery, whereas Parsonnet's method is applicable to all adult cardiac procedures but only uses mortality as an outcome. An overall score, the European system for cardiac operative risk evaluation (EuroSCORE), is another scoring system for assessing heart surgery based on databases in Europe,[6,7] and has been validated in further studies.[8–10] The Heart Center at the University Hospital in Linköping, Sweden, uses the Cleveland Model (Higgins score).

Several factors affect the outcomes and prognosis of cardiac surgery including the severity of cardiovascular disease, age, gender, and comorbid conditions. Factors related to how experienced the surgeons and other staff members are, have an effect on the level of surgical and anesthesia-related complications as well as other complications. Furthermore, compliance with medical treatments is important for long-term results. Multivariate analyses of possible risk factors for postoperative complications such as superficial and deep sternal wound complications/mediastinitis[11] and early and delayed cerebral complications[12] have been performed at the Heart Center. The aim has been to identify individual patients at risk as well as high-risk groups, and thus make it possible to apply strategies to reduce the risk and improve the quality of care.

Canonical correlation analysis (CCA) was developed by Hotelling (1935, 1936),[13] and can be viewed as an extension of multiple regression to situations involving more than one single response variable.[14,15] CCA is an exploratory technique for analyzing the relationship between two sets of variables, where each set can contain several variables. The method measures the total linear relationship between the two sets of multidimensional variables. The two resulting linear combinations, one of the x-variables and one of the y-variables, are called the first canonical variables or the first pair of canonical variables. CCA finds the coordinate system that is optimal for correlation analysis. Canonical correlations are invariant to scaling of the variables.

The aim of this study was to apply canonical correlation analysis (CCA) to explore the relationship of sets of multiple potential risk factors to sets of multiple clinical outcomes (as an extension of multiple regression analysis) in the field of cardiac surgery. The CCA method was also applied to the outcome variables of the Cleveland Model (Higgins score) as a reference model. The usability of CCA as a method for analysis and interpretation of risk factors and clinical outcomes is discussed.

MATERIAL AND METHODS

Study Population and Definition of Outcomes

From July 1996 through September 1999, 2605 adult patients underwent cardiac surgery at the University Hospital in Linköping, Sweden. Major postoperative complications were referred back to the University Hospital, as this is the only hospital in the southeastern health care region at which cardiac surgery is performed. The catchment area comprises of approximately 950,000 people and nine referring hospitals. Standard cardiopulmonary bypass (CPB) technique was used for the majority of patients. Three outcome variables were measured: (1) superficial and deep sternal wound complications/mediastinitis, (2) early and delayed cerebral complications, and (3) perioperative myocardial infarctions (PMIs). Criteria for defining and reporting surgical site infections (SSIs) were published in evidence-based guidelines by the Centers for Disease Control and Prevention (CDC) in 1999.[16] Briefly, superficial SSIs involve only skin or subcutaneous tissues, deep SSIs involve deep soft tissues (fascial and muscle layers), and organ/space SSIs involve tissues other than the incision. According to these definitions, postoperative mediastinitis is an organ/space SSI. Cerebral complications were defined as stroke, transient ischemic attack (TIA), or coma that could not be attributed to other neurological or metabolic disorders, hypoxia, anesthesia, or postoperative analgesia. This is in accordance with the definition of neurologic outcome "Type I" by Roach *et al.*[17] Cerebral complications were further classified as 'early' if cerebral symptoms were present after emergence from anesthesia and if the damage was considered to have occurred intraoperatively, and as 'delayed' if an interval of time elapsed before the cerebral symptoms occurred. There was also a group of patients in whom the onset of cerebral complications was unknown. Perioperative myocardial infarctions (PMIs) (i.e. clinical onset of pain, ECG changes, elevated cardiac enzymes) occurring in patients before discharge, were also evaluated in this study. ECG criteria included appearance of new Q-waves in at least two adjacent leads or the appearance of pathologic R-wave progression together with inversion of T-waves in at least two leads on a 12-lead ECG. Enzyme criteria included ASAT exceeding $3.0\,\mu$kat/L with ALAT less than half of the ASAT value, usually supported by CK-MB $> 70\,\mu$g/L on the first postoperative morning or by sustained elevation of troponin-T $> 2.0\,\mu$g/L on the third-fourth postoperative day.

Data Sources

Clinical and administrative data were collected from the patient records and cardiac surgery databases. Three databases from previous studies (Table I) were combined to form the final database from which the numerical calculations were performed. Seventy-four preoperative, intraoperative, and postoperative variables that might be associated with complications after cardiac surgery were evaluated. A complete list of all variables examined and their brief definitions are shown in Appendix I. Multivariate analyses of risk factors for superficial and deep sternal complications/mediastinitis as well as all, early, and delayed cerebral complications were performed in two earlier studies at the Heart Center,[11,12] and for perioperative myocardial infarctions analyses were performed on the present material.

Statistical Analysis

Differences in absolute frequencies between patients with and without complications with respect to sample size were analyzed using the Pearson chi-square statistic, and differences in mean values were analyzed using a two-tailed Student's *t*-test. Univariate analysis was performed followed by backward stepwise multivariate logistic regression analysis to derive risk factors for perioperative myocardial

Table I. Risk Factors for Perioperative Complications after Cardiac Surgery

Superficial sternal wound complications and deep sternal infections/mediastinitis [Ref. 11][a]			Cerebral complications (stroke, TIA or coma) [Ref. 12][b,c]			Perioperative myocardial infarctions (PMIs)[d,e]
Sternal wound complications 291 (9.7%)	Superficial sternal wound complications 194 (6.4%)	Deep sternal infections/mediastinitis 47 (1.6%)/50 (1.7%)	Cerebral complications 107 (3.3%)	Early cerebral complications 60 (1.8%)	Delayed cerebral complications 33 (1.0%)	Perioperative infarctions 100 (3.8%)
Obesity (BMI ≥ 30)	Age category (years) <75	Obesity (BMI ≥ 30)	Age category (years) >74	Age category (years) >74	Female gender	Angina
Insulin-dependent diabetes	Obesity (BMI ≥ 30)	Insulin-dependent diabetes	Insulin-dependent diabetes	Hypertension on medication	Insulin-dependent diabetes	Cardiopulmonary bypass time (min)
Smoking		Smoking	Dialysis	Aortic aneurysm surgery	Cerebrovascular disease	Post-bypass hypotension
Ventilator support (hours)		Peripheral vascular disease	Hypertension on medication	Cardiopulmonary bypass time (min)	CABG+valve surgery	Ventilator support (hours)
		NYHA score (≥3)	Cerebrovascular disease	Post-bypass hypotension	Ventilator support (hours)	Arrhythmia in ICU
		Bilateral use of IMA	Peripheral vascular disease	Arrhythmia in ICU	Supraventricular tachyarrhythmia in thoracic unit	Supraventricular tachyarrhythmia in thoracic unit
		Ventilator support (hours)	Aortic aneurysm surgery	Supraventricular tachyarrhythmia in thoracic unit		
			Cardiopulmonary bypass time (min)			
			Post-bypass hypotension			
			Ventilator support (hours)			
			Supraventricular tachyarrhythmia in thoracic unit			

24[f]	24[f]	24[f]	37[f]	30[f]	18[f]	29[f]
2401[g]	2401[g]	2401[g]	2535[g]	2514[g]	2742[g]	2086[g]
0.99[h]	0.56[h]	0.83[h]	0.85[h]	0.62[h]	0.90	0.91[h]
0.64[i]	0.62[i]	0.82[i]	0.85[i]	0.87[i]	0.84[i]	0.84[i]

The number of univariate variables included in the multivariate analyses are shown and, because of missing data, the sample size for each model. BMI: body mass index (kg/m^2); CABG: coronary artery bypass grafting; Cerebrovascular disease: any transient ischemic attack, reversible ischemic neurologic deficit, cerebrovascular accident/stroke, or history of cerebrovascular surgery; ICU: intensive care unit; IMA: internal mammary artery; NYHA: New York Heart Association (functional class I-IV); Peripheral vascular disease = history of aneurysm and/or occlusive arterial disease with or without surgical treatment; Post-bypass hypotension: systolic arterial pressure <90 mm Hg, ≥ 4 min, at cardiopulmonary bypass completion and soon after CPB; Smoking : current or during the last month before surgery.

[a] $n = 3008$ (01.96–09.99).

[b] $n = 3282$ (07.96–06.00).

[c] In 14 (0.4%) patients the onset of cerebral complications was unknown.

[d] $n = 2605$ (07.96–09.99).

[e] Odds ratios and confidence intervals for PMIs are presented in Table II.

[f] Univariate variables.

[g] Sample size (cases).

[h] Hosmer and Lemeshow test (H&L).

[i] Receiver operating characteristics (ROC) curve.

infarctions. p-Values of <0.05 were considered to indicate statistical significance on two-tailed testing. Statistical precision, the goodness of fit of the logistic model was evaluated by the Hosmer and Lemeshow test. Statistical accuracy, or model discrimination was assessed with the area under the ROC curve (c-value) computed by means of non-parametric methods for the model. Canonical correlation analysis (CCA) was applied to study sets of potential risk factors in relation to sets of clinical outcomes. Only the first canonical correlation (the highest possible correlation on the x-variable and y-variable side) has been used. All variables used in the canonical analyses are shown in Appendix I. The CCA equation is briefly explained in Appendix II. Statistical analyses were performed using the SPSS statistical package version 9.0 and Matlab version 6.5 for the CCA.

Significance of the canonical correlations was tested with randomization tests.[18,19] Under the null-hypothesis the x- and y-variables are uncorrelated, 100,000 random permutations of the y-variables were generated to estimate the distribution of canonical correlations. Robustness of the estimates of the canonical loadings was tested with bootstrapping.[19] With sampling sizes identical to those of the original data, 100,000 random samplings (with replacements) of the data were performed. For each sampling, the canonical loadings were calculated and the standard deviations of these estimates were calculated.

RESULTS

Clinical Findings

The results of the backward stepwise multivariate logistic regression analysis of perioperative myocardial infarction (PMI) are shown in Table II. Preoperative characteristics of the patients and surgical characteristics for patients with complications

Table II Backward Stepwise Multivariate Logistic Regression Analysis of Perioperative Myocardial Infarction (PMI)

	Patients with PMI [$n = 100/2605$ (3.8%)]	
Risk factors	OR (95%CI)	$p(<0.05)$*
Preoperative		
Angina	4.08 (1.80–9.25)	<0.001
Intraoperative		
Cardiopulmonary bypass time (min)	1.008 (1.004–1.013)	<0.001
Post-bypass hypotension (systolic arterial pressure <90 mm Hg, ≥4 min)	3.10 (1.78–5.41)	<0.001
Postoperative		
Ventilator support (h)	1.002 (1.0001–1.005)	0.045
Arrhythmia in ICU	3.26 (1.82–5.85)	<0.001
Supraventricular tachyarrhythmia in thoracic unit	1.79 (1.05–3.06)	0.033

Note. CI: confidence interval; OR: odds ratio; ICU: intensive care unit; Post-bypass hypotension: at cardiopulmonary bypass completion and soon after CPB. The number of univariate variables included in the multivariate analysis was 29. The sample size for the model was 2086, because of missing data. The Hosmer and Lemeshow test was 0.91, and ROC curve was 0.84.
*p-values <0.05 are shown. Reported p-values are two-sided.

(i.e. sternal wound complications/mediastinitis, cerebral complications or perioperative myocardial infarctions) are summarized in Table III and compared with data for patients without any of these complications. The median age was 67.0 years (range 16 to 87 years), and 72.2% were men, and 27.8% women. The distribution of procedures was 1840 (70.6%) CABGs, 205 (7.9%) combined CABG and valve procedures, 447 (17.2%) valve procedures, 48 (1.8%) aortic aneurysm procedures, and 65 (2.5%) other procedures including repair of atrioseptal defects, ventriculoseptal defects, and removal of atrial myxoma. The incidences of sternal wound complications/mediastinitis, cerebral complications, and perioperative myocardial infarctions according to the type of surgical procedure are shown in Table IV.

Complications

All surgical complications and their frequencies for the 2605 patients are listed in Table V. The total frequency of complications after cardiac surgery was 37.7%. Supraventricular tachyarrhythmia, a common postoperative complication after cardiac surgery, appeared in 23.3% of the patients, 36.6% of whom underwent combined procedures, 30.4% valve procedures, and 10.8% off-pump procedures (OPCABG). Perioperative myocardial infarction, cerebral complications or sternal wound complications/mediastinitis occurred in 16.6% of the patients. Eleven of the patients had both a sternal wound complication and a cerebral complication, ten patients had a sternal wound complication and a perioperative myocardial infarction, and in nine cases the patients suffered both a cerebral complication and a perioperative myocardial infarction. In the 85 patients with cerebral complications, 21(24.7%) of the symptoms were transient, and in 64(75.3%) patients the symptoms were permanent. These patients were on average 5 years older (70.7 ± 8.6 years) compared to those without cerebral complications. Ninety-three of the infected patients needed surgical revisions, and 26 of the patients needed two or more revisions and antibiotics before the infection was cured. The mean preoperative NYHA score was 3 (range 1–4) and the Higgins score was 2.8 (range 0–19) for all patients.

The patients who suffered these complications also had prolonged operation time, cardiopulmonary bypass time, and aortic cross clamp-time (see Table III). Postoperative ventilator support times averaged 50.4 h in the complication group versus 13.8 h for patients without any of these three complications ($p < 0.001$), as illustrated in Table III. The average intensive care stay was 3.7 days for the complication group versus 1.5 days in the other group ($p < 0.001$). The complication group was more likely to receive blood transfusions than the other group (48.8% versus 31.2%, $p < 0.001$). The reoperation rate for control of bleeding in this group was also higher (6.5% versus 4.1%, $p = 0.041$). These patients were also in need of more intravenous nitroglycerin ($p < 0.001$), inotropic support ($p < 0.001$), metabolic support ($p < 0.001$), and use of the intraaortic balloon pump ($p < 0.001$).

The 30-day mortality rate for all patients was 65/2605(2.5%), and the 1-year mortality rate was 122/2605(4.7%). Patients who died were approximately 5 years older than survivors (70 years versus 65 years). The 30-day mortality was 23.5% for all patients with cerebral complications, 15.2% for those with perioperative myocardial infarctions, and 0.7% for patients with sternal wound

Table III Preoperative Patient Characteristics, Surgical Characteristics, and Postoperative Data[a,b]

Variables	Patients without complications ($n = 2172$)	Patients with complications ($n = 433$)	p-value
Preoperative			
Mean age (year)	65.5 ± 10.5	65.8 ± 9.9	
Female/male	595/1577	130/303	
Obesity (BMI ≥ 30)	295 (13.6)	97 (22.5)	<0.001
Diabetes on medication	266 (12.3)	95 (22.0)	<0.001
Smoking	1019 (49.8)	209 (52.5)	
COPD	124 (5.8)	29 (6.8)	
Hypertension	771 (36.3)	178 (42.1)	0.028
Prior MI (myocardial infarction)	996 (49.6)	210 (49.2)	
Heart failure	384 (18.0)	82 (19.2)	
Unstable angina	795 (36.9)	178 (41.4)	
Prior cerebrovascular disease	123 (6.0)	35 (8.7)	0.045
Prior peripheral vascular disease	135 (6.4)	46 (10.9)	0.002
NYHA score (≥3)	1526 (74.7)	327 (81.8)	0.002
Higgins score (≥5)	427 (19.7)	114 (26.3)	0.002
Severe LV dysfunction	116 (5.4)	33 (7.7)	
Anemia (hemoglobin ≤ 110 g/L)	123 (5.7)	39 (9.0)	0.012
Serum creatinine (≥168 μmol/L)	51 (2.4)	12 (2.8)	
Prior cardiac surgery	103 (4.7)	30 (6.9)	
Prior PTCA	180 (8.3)	55 (12.8)	0.004
Intraoperative			
Emergency surgery	113 (5.2)	43 (10.0)	<0.001
Duration of surgery (>300 min)	95 (4.6)	54 (13.2)	<0.001
Aortic cross clamp-time (min)	56.9 ± 32.9	61.7 ± 35.7	0.011
Cardiopulmonary bypass time (min)	91.4 ± 39.4	111.0 ± 59.5	<0.001
Offpump	58 (2.7)	16 (3.7)	
Number of distal anastomoses (≥3)	1305 (63.1)	268 (64.4)	
Single/bilateral use of IMA	1570 (74.7)	319 (76.1)	
Need for inotropic support	217 (10.0)	83 (19.2)	<0.001
Need for metabolic support	208 (9.6)	97 (22.4)	<0.001
Need for mechanical support	9 (0.4)	3 (0.7)	
Postoperative			
IABP	19 (0.9)	20 (4.6)	<0.001
Reoperation bleeding	90 (4.1)	28 (6.5)	0.041
Red blood cells (units)	1.2 ± 2.8	3.0 ± 5.5	<0.001
Need for metabolic support	164 (7.6)	95 (21.9)	<0.001
Ventilator support (h)	13.8 ± 38.8	50.4 ± 105.7	<0.001
Arrhythmia in ICU	225 (10.4)	92 (21.2)	<0.001
Supraventricular tachyarrhythmia in thoracic unit	460 (21.2)	144 (35.5)	<0.001
Average length of stay in ICU (days)	1.5 ± 2.2	3.7 ± 5.3	<0.001
Average length of stay (days)	8.8 ± 3.6	10.9 ± 6.0	<0.001

Note. BMI: body mass index (kg/m^2); Cerebrovascular disease: Any transient ischemic attack, reversible ischemic neurologic deficit, cerebrovascular accident/stroke, or history of cerebrovascular surgery; COPD: chronic obstructive pulmonary disease on medication; Emergency surgery: Patients admitted from the catheterization laboratory or the coronary care unit who had surgery within hours; Higgins score[(2)]—the Cleveland Clinic Risk Severity Score (CCRSS); IABP: intraaortic balloon pump; ICU: intensive care unit; IMA: internal mammary artery; LV: left ventricular; NYHA: New York Heart Association (functional class I–IV); Peripheral vascular disease: History of aneurysm and/or occlusive arterial disease with or without surgical treatment; PTCA: percutaneous transluminal coronary angioplasty; Smoking: Current and during the last month before surgery.

[a]Complications include sternal wound complications/mediastinitis, cerebral complications or perioperative myocardial infarctions.

[b]Data presented are mean ± SD or number (percentage) of patients.

*p-values <0.05 are shown. Reported p-values are two-sided.

Table IV Incidence of Sternal Wound Complications/Mediastinitis, Cerebral Complications, and Perioperative Myocardial Infarctions by Type of Procedure

Procedure	Total no.	Percentage	Sternal wound complications/ mediastinitis	Cerebral complications	Perioperative myocardial infarctions
CABG	1840	70.6	214 (11.6)	40 (2.2)	70 (3.8)
CABG+valve surgery	205	7.9	18 (8.8)	19 (9.3)	15 (7.3)
Valve surgery	447	17.2	35 (7.8)	13 (2.9)	8 (1.8)
Other procedures	113	4.3	8 (7.1)	13 (11.5)	7 (6.2)
Total	2605	100.0	275 (10.6)	85 (3.3)	100 (3.8)

Note. Other procedures include repair of atrioseptal defect and ventriculoseptal defect, removal of atrial myxoma, and graft repair of the ascending aorta.
Percentage values are shown in parenthesis.

complications/mediastinitis. The 30-day mortality rate was higher in women than in men (3.9% versus 2.0%, $p = 0.007$), as was the 1-year mortality rate (6.3% versus 4.0%, $p = 0.017$).

Canonical Correlation Analysis

Canonical correlation analysis was performed to examine the association between a set of independent (x) variables and a set of more than one dependent (y) variable in different models. Table VI gives the canonical correlation and individual

Table V Surgical Complications ($n = 2605$).

Complication		n	Percentage
Operative	Reoperation (bleeding/tamponade)	118	4.5
	Reoperation (valve dysfunction)	9	0.3
	Perioperative myocardial infarction (PMI)	100	3.8
Infection	All sternal wound complications	275	10.6
	Superficial sternal wound complication	182	7.0
	Deep sternal infection/mediastinitis	93	3.6
	Septicemia	34	1.3
Neurologic	Cerebral complications[a]	85	3.3
	Early cerebral complication	49	1.9
	Delayed cerebral complication	24	0.9
Pulmonary	Prolonged ventilator support	81	3.1
	Pneumonia	78	3.0
Renal	Renal insufficiency	86	3.3
	Dialysis required	26	1.0
Other	Permanent pacemaker	22	0.9
	Multiple organ failure	33	1.3
	Tachycardia in ICU	286	11.0
	Tachyarrhytmia in ICU	317	12.2
	Supraventricular tachyarrhythmia in thoracic unit	604	23.3

ICU: Intensive care unit.
[a]In 12 (0.5%) patients the onset of cerebral complications was unknown.

Table VI The First Variables in the Listing Provide the Greatest Amount of Explanatory Power on the (Independent) x-Variable and the (Dependent) y-Variable Side

Canonical loadings					
		SD			SD
MODEL I[a]					
Risk factor set: 65 x-variables			Outcome set: 7 y-variables		
Ventilator support (h)	0.71	0.08	Perioperative myocardial infarction	0.72	0.14
Units of red blood cells	0.67	0.07	Cerebral complication	0.66	0.11
Duration of surgery	0.57	0.06	Early cerebral complication	0.56	0.15
Metabolic support in ICU	0.54	0.08			
Metabolic support GIK in ICU	0.51	0.08			
Cardiopulmonary bypass time (min)	0.48	0.06			
Arrhythmia in ICU	0.48	0.06			
MODEL II[b]					
Risk factor set: 64 x-variables			Outcome set: 12 y-variables		
Units of red blood cells	0.86	0.07	Length of stay in intensive care unit (days)	0.89	0.04
Units of platelets/fresh frozen plasma/stored plasma	0.67	0.08	Ventilator support (h)	0.86	0.04
Arrhythmia in ICU	0.57	0.06	Renal insufficiency	0.61	0.06
Duration of surgery	0.53	0.06	Multiple organ failure	0.54	0.09
Cardiopulmonary bypass time (min)	0.51	0.06	Dialysis	0.53	0.08
Metabolic support in ICU	0.45	0.08	30-day mortality	0.51	0.06
Blood transfusion	0.45	0.08	Pneumonia	0.44	0.06

Note. GIK: glucose-insulin-potassium; ICU: intensive care unit; SD: standard deviation.

[a]Canonical correlations: $r = 0.53$ (sample size: 1843; $p < 0.001$). The outcome variables included are all seven complications from Table I, and all independent x-variables that were selected by univariate analyses ($p < 0.15$) and included in backward stepwise multivariate logistic regression analyses for these outcomes (see Appendix I). In this model ventilator support (hours) and multiple organ failure are considered and included in the analysis as preoperative independent x-variables according to earlier multivariate regression analyses.

[b]Canonical correlations: $r = 0.76$ (sample size: 1802; $p < 0.001$). The outcome variables included are all complications in MODEL II (see Appendix I), and all independent x-variables shown in the same appendix. Ventilator support (hours) and multiple organ failure are considered and included in the analysis as dependent y-variables.

correlations (loadings) between the risk factor variables and their canonical variable, and between the outcome variables and their canonical variable, for Models I and II. Model I is based on all independent x-variables (risk factors) that were previously selected by univariate analyses ($p < 0.15$)[11,12]and included in multivariate logistic regression analyses of three serious outcomes after cardiac surgery (see Table I). Model II in Table VI consists of a larger set of y-variables than in Model I. In Model I, mainly intraoperative and postoperative risk factors are associated with three outcomes, and in Model II intraoperative and postoperative risk factors are associated with seven outcomes (see also Fig. 1). The absolute magnitude of loadings of preoperative, intraoperative, and postoperative risk factor variables in Model II are shown in Fig. 2. The relative contributions of these three groups of variables to the corresponding canonical correlation vector is thus illustrated, showing

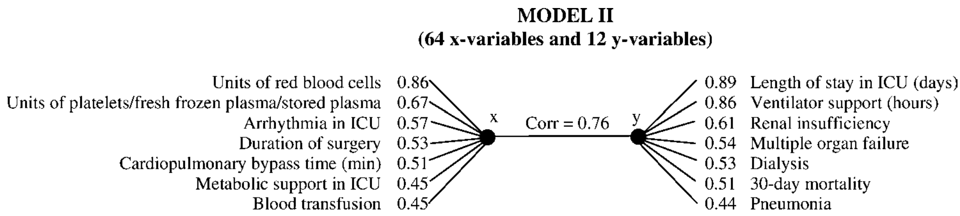

Fig. 1. The first canonical correlations in Model II (Table VI) showing the canonical correlation (0.76) and the loadings on the x-side and the y-side. All variables are not included in this figure. ICU: Intensive care unit.

that postoperative variables generally have higher loadings than intraoperative variables, which in turn have higher loadings than preoperative variables. Higgins score, as a preoperative risk factor, had the highest loading (0.38) against outcomes (Model II), showing a weak predictive ability of preoperative variables. The predictive ability of sternal wound complications/medistinitis was also low in both models.

In Table VII, models based on the Cleveland model (Higgins score)[2] are used as reference material in three models. First, a basic model with Higgins morbidity— and mortality-associated preoperative risk factors is shown. Thereafter the correlation between several possible risk factors and Higgins outcomes for morbidity and mortality were examined by using intraoperative and postoperative risk factors, separately. The results of intraoperative and postoperative risk factors in relation to Higgins outcome are quite similar to the results in Model II (Table VI).

Metabolic support, metabolic support with GIK, and metabolic support with amino acids as well as blood transfusion, units of red blood cells, and units of platelets/fresh frozen plasma/stored plasma were included in both models with some degree of redundancy. The rationale behind the use of both dichotomized and

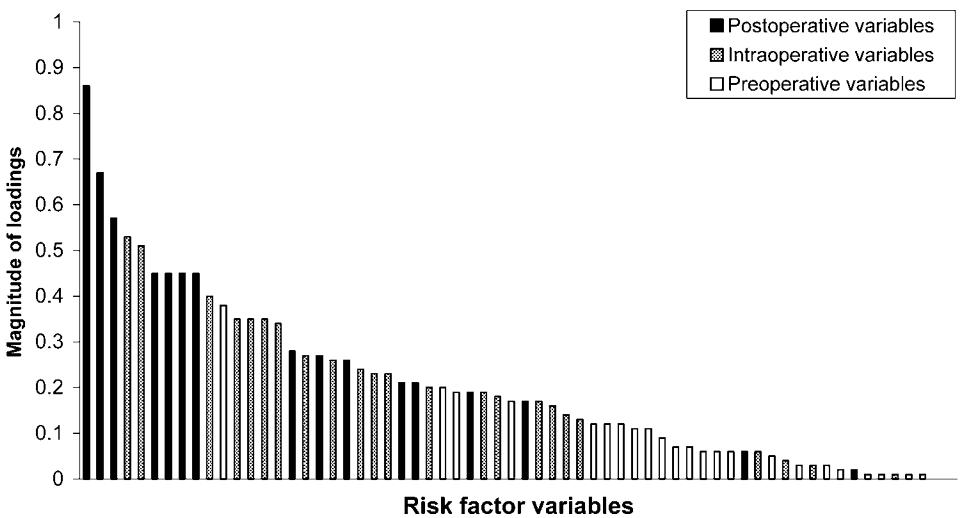

Fig. 2. The magnitude of loadings for preoperative, intraoperative, and postoperative risk factor variables in Model II (Table VI).

Table VII Models based on Higgins score [2]. Higgins outcomes (morbidity and mortality). The First Variables in the Listing Provide the Greatest Amount of Explanatory Power on the (Independent) x-Variable and the (Dependent) y-Variable Side. Preoperative, Intraoperative, and Postoperative Variables are Included, Separately, in the Models below, and Show Increasing Correlation Values

	Canonical loadings	SD		Canonical loadings	SD
PREOPERATIVE VARIABLES[a,d]					
Risk factor set: 13 x-variables			Outcome set: 6 y-variables		
Emergency surgery	0.62	0.16	Lung complication	0.78	0.12
Hemoglobin level	0.59	0.10	30-day mortality	0.68	0.11
Mitral valve insufficiency	0.41	0.13	Cerebral complication	0.56	0.13
Prior cardiac surgery	0.35	0.14	Dialysis	0.47	0.14
Age	0.32	0.10	Perioperative myocardial infarction	0.42	0.11
INTRAOPERATIVE VARIABLES[b,d]					
Risk factor set: 23 x-variables			Outcome set: 6 y-variables		
Duration of surgery	0.79	0.04	Perioperative myocardial infarction	0.73	0.07
Cardiopulmonary bypass time (min)	0.73	0.05	Lung complication	0.70	0.07
Metabolic support GIK	0.60	0.05	30-day mortality	0.55	0.07
Metabolic support	0.57	0.05	Dialysis	0.48	0.10
Inotropic support	0.53	0.05	Cerebral complication	0.44	0.07
Post-bypass hypotension (soon after CPB)	0.50	0.05			
Post-bypass hypotension (at CPB completion)	0.48	0.05			
Use of desmopressin	0.48	0.06			
POSTOPERATIVE VARIABLES[c,d]					
Risk factor set: 16 x-variables			Outcome set: 6 y-variables		
Units of red blood cells	0.88	0.03	Lung complication	0.81	0.04
Units of platelets/fresh frozen plasma/stored plasma	0.70	0.04	Perioperative myocardial	0.56	0.06
Arrhythmia in ICU	0.59	0.04	30-day mortality	0.56	0.05
Metabolic support in ICU	0.52	0.05	Dialysis	0.55	0.08
Metabolic support GIK in ICU	0.51	0.05	Cerebral complication	0.41	0.05
Blood transfusion	0.47	0.03			
IABP (intraaortic balloon pump)	0.39	0.07			

Note. GIK: glucose-insulin-potassium; ICU: intensive care unit; SD: standard deviation.
[a]Canonical correlations: $r = 0.26$ (sample size: 2383) $p < 0.001$.
[b]Canonical correlations: $r = 0.48$ (sample size: 2237) $p < 0.001$.
[c]Canonical correlations: $r = 0.63$ (sample size: 2440) $p < 0.001$.
[d]The outcome variables included are Higgins morbidity and mortality variables (see Appendix 1), and all independent x-variables shown in the same appendix. Emergency surgery is considered and included in the analysis as a preoperative independent x-variable.

continuous variables for metabolic support and blood transfusion is that the CCA method can handle interdependent risk factors and provide information about their relative importance through the individual correlations or loadings. The results indicate that the quantitative aspects of blood transfusion (units of blood cells and plasma) have higher loadings than the qualitative aspects (blood transfusion as dichotomized yes/no), while for metabolic support the opposite results were obtained.

The randomization test gave a significance $p < 0.001$ for all models. The confidence interval for the null-hypothesis (that there is no correlation) for $p = 0.001$ is 0.40 for model I and 0.47 for model II in a one-sided test of the absolute value of the correlation. (Note that the sign of the canonical correlation does not have any meaning.) The estimated canonical correlations (0.53 and 0.76, respectively) are well above these limits (see Table VI). The standard deviations of the estimated canonical loadings are also listed in Table VI.

DISCUSSION

The challenge of outcome analysis for health care providers is to be able to measure relevant outcome variables and relate those to patient risks. There is no formal consensus about what data should be collected, the exact definitions of data and outcomes, or how these outcomes should be risk assessed. Many measurement processes are therefore influenced by local factors such as the places where and the times when events take place.[1,8,20] Risk indexes are more applicable to patient populations where the patient characteristics and clinical guidelines are comparable to those of the original environments. Orr *et al.*[21] compared four severity-adjusted models for predicting mortality after CABG surgery and found a striking variation in the mortality rate in their population as predicted by the different models (2.8–9.2%). The authors suggested that further studies must investigate the complex interplay of preoperative, intraoperative, and postoperative factors when attempting to quantitate CABG outcomes. Physicians have to be very cautious when applying predictive indexes to individual patients as the score produces a probability (i.e. a 20% risk of complications), but individual outcomes are binary (i.e. the patient will either have or not have a complication).

The present study has some limitations. Retrospective studies using existing clinical data may be compromised by missing data or inexact definitions. Data on postoperative heart failure were not available in the cardiothoracic database. In certain circumstances it is sometimes difficult to decide whether the variables are the cause or the effect of the outcome (i.e. prolonged ventilator support, atrial fibrillation), especially as some complications appear before and some after the event. Prolonged time on a ventilator has been shown to increase the likelihood of sternal infections due to extended exposure to risk factors in the ICU environment because of a prolonged stay and subsequent microbial colonization of patients.[11,16] Arrhythmias (mainly atrial fibrillation) can be a precipitating event in patients who suffer cerebral complications, but can also appear after the cerebral complication.[12,17] This study does not identify whether excessive blood transfusion is a partial cause or an effect of increased length of stay in the ICU, but the two variables seem related. The database could not provide adequate information about whether the blood transfusions were given mainly intra- or postoperatively. Preoperative and surgical characteristics that contribute to the clinical outcome can be quite different in different Heart Centers, and therefore results from one institution cannot be broadly generalized to others.

Multiple logistic regression is one method that can be used to determine the relative importance of simultaneous risk factors.[1–6] A physician may want to study the relationship of various risk factors to multiple outcomes. Canonical correlation analysis can be used in situations involving more than one single response variable. The aim of CCA is to determine the magnitude of relationships between two sets of variables and to derive weights for each set of variables (risk factor, outcome) that yield maximum correlation for each linear composite. Canonical correlation evaluates the relative contribution of each variable to the derived functions in order to explain the nature of the relationships. The canonical correlation value is the correlation between the linear composites, not the correlation with individual variables, while the loadings show the correlations between the individual variables and their composite. One consequence of looking at loadings for model interpretation is that multicollinearity (when the variables in the analysis are correlated among themselves) does not disturb the interpretation. This is in contrast to more common multivariate statistics like multiple regression, where interpretation normally is based on significance of the weights, which is highly influenced by multicollinearity (if two variables have a high correlation one of them may be almost completely eliminated even if both have a high correlation to the outcome). The interaction between the selected variables in this study was measured and interpreted for information.

It is important to have an understanding of the statistical models from a clinical perspective, and how they could be applied in practice. The CCA method was therefore applied to previous results of multivariate logistic regression equations (Table I) that related various independent variables to the probability of complications after cardiac surgery. In the multivariate regression analyses preoperative risk factors such as age, obesity, hypertension on medication, diabetes on medication, smoking, and peripheral vascular disease were commonly associated with an increased risk of complications. Intraoperative risk factors appeared to be aortic aneurysm surgery, prolonged cardiopulmonary bypass time, and post-bypass hypotension. Postoperative risk factors were prolonged ventilator support, arrhythmia in the ICU, and supraventricular tachyarrhythmias in the cardiothoracic unit.

In the multivariate regression analyses a few preoperative variables were associated with sternal wound complications/mediastinitis and with cerebral complications, but only one preoperative risk factor was associated with perioperative myocardial infarction. In the canonical correlation analysis intraoperative and postoperative risk factors seem to be more associated with perioperative myocardial infarction. Prolonged cardiopulmonary bypass and surgery are often associated with more difficult cases with more advanced atherosclerotic disease or severe valvular calcification. In a case control study, Dahlin *et al.*[22] concluded that poorer conditions for revascularization may explain some of the perioperative myocardial infarctions and requirements for prolonged cardiopulmonary bypass time and surgery, and also difficulties in weaning the patient from cardiopulmonary bypass. In patients with low cardiac output and in those with evidence of neurologic deficits, inotropic support and metabolic support as well as prolonged ventilatory support are often necessary.[23,24] This is in accordance with Model I (Table VI).

The CCA method provides an overall picture of associations between risk factors and outcome variables, with information about the relative contributions to the corresponding canonical correlation vector through the individual correlations or loadings. In Fig. 2 the distribution of pre-, intra- and postoperative loadings are presented for model II, and as can be seen, postoperative and intraoperative variables have generally higher loadings than preoperative variables. Of the preoperative variables, Higgins score, hemoglobin level, and serum creatinine level have the highest loadings. Aortic aneurysm surgery and combined CABG and valve surgery had the highest incidences of perioperative myocardial infarctions as well as cerebral complications (Table IV). Patients who underwent these complex procedures more often suffered perioperative myocardial infarctions and cerebral complications, and also needed more blood transfusions and prolonged ventilator support. The predictive ability of infections (i.e. sternal wound complications/mediastinitis) was weak (loading < 0.3) in both models, and also in the models based on Higgins outcomes for morbidity and mortality. Sternal wound complications/mediastinitis often had a late onset (weeks to months after discharge) according to our previous study.[11]

The second model with 12 clinical outcomes and possible risk factors showed a higher correlation than the first model. Risk factors for perioperative morbidity and mortality may be cumulative and interrelated. If one organ fails, it may influence the function of another organ. Prolonged length of stay in the ICU may reflect persistent LV dysfunction with hemodynamic instability, postoperative bleeding, arrhythmias, fluid overload or renal failure. The outcome variables added in model II, such as renal insufficiency, dialysis, multiple organ failure, and pneumonia may be a consequence of perioperative myocardial infarction and cerebral complications seen in Model I (Table VI).

By using Higgins outcome for morbidity and mortality and by adding further variables separately (Table VII), first intraoperative and then postoperative variables, the canonical correlations were increased. These results are in accordance with findings from the Cleveland Clinic,[25] where they developed a complementary model to their previously reported preoperative model,[2] also taking intraoperative events into consideration (ROC curve 0.87). Higgins, *et al.*[25] conclude that the ability to predict outcome with an ICU admission score enhances preoperative risk stratification, and that sequential scoring allows updated prognoses at different points in the continuum of care. The authors suggest that the impact of ICU admission on the physiology and operative events should be considered in assessing postoperative outcome. Canonical correlation analysis in our study also suggested the importance of intraoperative and postoperative risk factors in relation to outcomes. Thus, computation of loadings for risk factors can provide unique information.

The strength of CCA as compared to multiple regression analysis is its ability to generate a linear combination of risk factors and outcome variables that have the highest possible correlation for the given data set. A linear combination of risk factors might be used as a more robust predictor of an outcome variable, and a linear combination of outcome variables might have a higher correlation with the risk factors as compared to a single outcome variable. In some risk models (e.g. the Cleveland model, Higgins score) logical combinations of dichotomized output variables are constructed (such as mortality, or symptom1, or symptom2, etc.). Even if the rationale for such constructed outcome variables is based on sound clinical knowledge, from a mathematical perspective they are ad hoc solutions. With the

CCA method, new linear output combinations are constructed that can be proven to have the highest possible correlation with the risk factors. Many of the variables are not normally distributed. While this is not a problem for the canonical correlation analysis, it does make it difficult to use classical parametric methods for estimating statistical significance and confidence intervals. We have therefore used resampling techniques to address these issues. These methods also handle the problem that the variables are strongly correlated within the sets (x and y). The randomization tests showed a very high significance ($p < 0.001$) for the canonical correlation in both models. The standard deviations of the canonical loadings indicate that the estimates of the loadings are robust.

A result of special interest as compared to ordinary correlation analysis is the case of a high canonical correlation with a low and even distribution of individual correlations (or loadings), indicating a high correlation between the risk factors and the output vector that would have been missed without the CCA technique. The opposite case with an uneven distribution, with one variable with a very high loading and the rest with very low loadings, could be approximated with a single variable case that should have been discovered by ordinary analysis. The results presented in Tables VI and VII show a distribution with a slow decrease of loadings, implying that the predictive power of these models as compared to multiple regression models should be superior. On the other hand, these results offer a more complex clinical picture for analysis and interpretation. Forthcoming research will continue the work with construction of clinically accepted combinations of output variables for statistically robust prediction based on relevant sets of risk factors.

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APPENDIX I. VARIABLES IN CANONICAL CORRELATION ANALYSIS

Model I (65 *x*-variables and 7 *y*-variables)

Preoperative x-variables

Age in years as a continuous variable; gender; BMI, body mass index: (weight in kg)/(height in m);[2] diabetes, currently treated with oral medications or insulin; insulin-dependent diabetes; smoking, current or during the last month before surgery; COPD, chronic obstructive pulmonary disease on medication; hypertension on medication; angina; unstable angina; MI, myocardial infarction; endocarditis; heart failure; cerebrovascular disease, any transient ischemic attack, reversible ischemic neurologic deficit, cerebrovascular accident/stroke, or history of cerebrovascular surgery; peripheral vascular disease, history of aneurysm and/or occlusive arterial disease with or without surgical treatment; NYHA score, New York Heart Association (functional class I–IV); Higgins score[(2)]—the Cleveland Clinic Risk Severity Score (CCRSS); hemoglobin (g/L); serum creatinine (μmol/L); dialysis; severe LV (left ventricular) dysfunction; prior cardiac surgery; prior PTCA; preoperative length of stay (days).

Intraoperative x-variables

Priority of surgery (emergency surgery, patients admitted from the catheterization laboratory or the coronary care unit who had surgery within hours); type of operation: CABG, CABG + valve surgery, valve surgery, aortic aneurysm surgery, and other surgery; duration of surgery; cardiopulmonary bypass time; aortic cross clamp-time; off pump surgery; IMA, internal mammary artery; bilateral use of IMA; inotropic support; metabolic support; metabolic support GIK, glucose–insulin–potassium; pre-bypass hypotension (systolic arterial pressure <90 mmHg, ≥ 4 min, on induction and pre-bypass); post-bypass hypotension (systolic arterial pressure <90 mmHg, ≥ 4 min, at cardiopulmonary bypass completion and soon after CPB); use of tranexamic acid; use of aprotinin; use of desmopressin.

Postoperative x-variables

Reoperation (bleeding/tamponade); valve dysfunction; reoperation (valve dysfunction); IABP, intraaortic balloon pump; units of red blood cells; units of platelets/fresh frozen plasma/stored plasma; metabolic support; metabolic support GIK, glucose-insulin-potassium; metabolic support amino acids in ICU; SVO_2, mixed venous oxygen saturation, (60–80%) in ICU; use of tranexamic acid; use of aprotinin; use of desmopressin in ICU; ventilator support (hours); renal dysfunction; multiple organ failure; tachycardia in ICU; arrhythmia in ICU; supraventricular tachyarrhythmia in thoracic unit.

Outcomes y-variables

Superficial and deep sternal wound complications; superficial sternal wound complications; deep sternal infections/mediastinitis; all cerebral complications; early cerebral complications; delayed cerebral complications; and PMI, perioperative myocardial infarction.

Model II (64 *x*-variables and 12 *y*-variables)

Preoperative x-variables

Age in years as a continuous variable; gender; BMI, body mass index: (weight in kg)/(height in meters)^2; diabetes, currently treated with oral medications or insulin; insulin-dependent diabetes; smoking, current or during the last month before surgery; COPD, chronic obstructive pulmonary disease on medication; hypertension on medication; angina; unstable angina; MI, myocardial infarction; endocarditis; heart failure; cerebrovascular disease, any transient ischemic attack, reversible ischemic neurologic deficit, cerebrovascular accident/stroke, or history of cerebrovascular surgery; peripheral vascular disease, history of aneurysm and/or occlusive arterial disease with or without surgical treatment; NYHA score, New York Heart Association (functional class I–IV); Higgins score[(2)]–the Cleveland Clinic Risk Severity Score (CCRSS); hemoglobin (g/L); serum creatinine (μmol/L); dialysis; severe LV (left ventricular) dysfunction; prior cardiac surgery; prior PTCA; preoperative length of stay (days).

Intraoperative x-variables

Priority of surgery (emergency surgery, patients admitted from the catheterization laboratory or the coronary care unit who had surgery within hours); type of operation: CABG, CABG + valve surgery, valve surgery, and aortic aneurysm surgery; duration of surgery; cardiopulmonary bypass time; aortic cross clamp-time; off pump surgery; IMA, internal mammary artery; number of distal anastomoses; inotropic support; metabolic support; metabolic support GIK, glucose–insulin–potassium; metabolic support amino acids; need for nitroglycerin; pre-bypass hypotension (systolic arterial pressure <90 mmHg, ≥ 4 min, on induction and pre-bypass); post-bypass hypotension (systolic arterial pressure <90 mmHg, ≥ 4 min, at cardiopulmonary bypass completion and soon after CPB); use of tranexamic acid; use of aprotinin; use of desmopressin; left ventricular assist device.

Postoperative x-variables

Reoperation (bleeding/tamponade); reoperation (valve dysfunction); IABP, intraaortic balloon pump; blood transfusion; units of red blood cells; units of platelets/fresh frozen plasma/stored plasma; metabolic support; metabolic support GIK, glucose–insulin–potassium; metabolic support amino acids in ICU; SVO_2, mixed venous oxygen saturation, (60–80%) in ICU; use of tranexamic acid; use of aprotinin; use of desmopressin in ICU; tachycardia in ICU; arrhythmia in ICU; supraventricular tachyarrhythmia in thoracic unit.

Outcomes y-variables

Superficial and deep sternal wound complications; all cerebral complications; PMI, perioperative myocardial infarction ; ventilator support (hours); pneumonia; septicemia; renal insufficiency; dialysis; multiple organ failure; permanent pacemaker; length of stay in intensive care (days); 30-day mortality. ICU: intensive care unit.

MODELS BASED ON HIGGINS SCORE [2]

Higgins Outcomes (Morbidity and Mortality)

Outcomes y-variables (all three models)

PMI, perioperative myocardial infarction; infection (superficial and deep sternal wound complications/mediastinitis); all cerebral complications; lung complications (prolonged ventilator support); dialysis; 30-day mortality.

Preoperative x-variables

Emergency surgery; serum creatinine level ($\geq$168 μmol/L); reoperation (prior cardiac surgery); severe LV dysfunction; operative mitral valve insufficiency; age ($\geq$65 years and $\leq$74 years, $\geq$75 years); diabetes on medication; weight ($\leq$65 kg); anemia (hematocrit $\leq$34%/ hemoglobin $\leq$110 g/L); COPD on medication; cerebrovascular disease; operative aortic valve stenosis operated; prior vascular surgery (peripheral vascular disease).

Intraoperative x-variables

Type of operation: CABG, CABG + valve surgery, valve surgery, and aortic aneurysm surgery; duration of surgery; cardiopulmonary bypass time; aortic cross clamp-time; off pump surgery; IMA, internal mammary artery; number of distal anastomoses; inotropic support; metabolic support; metabolic support GIK, glucose–insulin–potassium; metabolic support amino acids; need for nitroglycerin; pre-bypass hypotension (systolic arterial pressure $<$90 mmHg, $\geq$4 min, on induction and pre-bypass); post-bypass hypotension (systolic arterial pressure $<$90 mmHg, $\geq$4 min, at cardiopulmonary bypass completion and soon after CPB); use of tranexamic acid; use of aprotinin; use of desmopressin; left ventricular assist device.

Postoperative x-variables

Reoperation (bleeding/tamponade); reoperation (valve dysfunction); IABP, intraaortic balloon pump; blood transfusion; units of red blood cells; units of platelets/fresh frozen plasma/stored plasma; metabolic support; metabolic support GIK, glucose–insulin–potassium; metabolic support amino acids in ICU; SVO_2 mixed venous oxygen saturation, (60–80%) in ICU; use of tranexamic acid; use of aprotinin; use of desmopressin in ICU; tachycardia in ICU; arrhythmia in ICU; supraventricular tachyarrhythmia in thoracic unit.

APPENDIX II. CANONICAL CORRELATION ANALYSIS

Canonical correlation analysis (CCA) is a generalization of the ordinary Pearson correlation coefficient to multi-dimensional variables. It measures the total linear relationship between two sets of multidimensional variables. CCA finds a linear combination of one set of variables that is the best predictor and another linear combination of another set of variables that is the most predictable.

Consider the projection of two multi-dimensional variables $\mathbf{x}$ and $\mathbf{y}$ onto the vectors $\mathbf{w}_x$ and $\mathbf{w}_y$, respectively. The correlation between the projections can be written as,

$$\rho = \frac{\mathbf{w}_x^{\mathrm{T}}\mathbf{C}_{xy}\mathbf{w}_y}{\sqrt{\mathbf{w}_x^{\mathrm{T}}\mathbf{C}_{xx}\mathbf{w}_x\mathbf{w}_y^{\mathrm{T}}\mathbf{C}_{yy}\mathbf{w}_y}} \qquad (1)$$

where $\mathbf{C}_{xx}$ and $\mathbf{C}_{yy}$ are the within sets covariance matrices of $\mathbf{x}$ and $\mathbf{y}$, respectively, and $\mathbf{C}_{xy}$ is the between sets covariance matrix. The extreme points of this quotient are given by the solutions to the two eigenvalue equations,

$$\begin{cases} \mathbf{C}_{xx}^{-1}\mathbf{C}_{xy}\mathbf{C}_{yy}^{-1}\mathbf{C}_{yx}\hat{\mathbf{w}}_x = \rho^2\hat{\mathbf{w}}_x \\ \mathbf{C}_{yy}^{-1}\mathbf{C}_{yx}\mathbf{C}_{xx}^{-1}\mathbf{C}_{xy}\hat{\mathbf{w}}_y = \rho^2\hat{\mathbf{w}}_y \end{cases} \qquad (2)$$

The eigenvalues ρ^2 are the squared *canonical correlations*, and the eigenvectors corresponding to the largest eigenvalue gives the maximum of Equation 1. The subsequent solutions maximize the correlation of the projection under the constraint that the projections are uncorrelated to the other components.

The *canonical loadings* measure the correlation between each component of the variables and the projection onto the corresponding canonical correlation vector, i.e. corr($x_{i,}$ $\mathbf{w}_x^{\mathrm{T}}\mathbf{x}$) and corr($\mathrm{y}_{i,}$ $\mathbf{w}_x^{\mathrm{T}}\mathbf{y}$) for the x- and y-components, respectively. This is a measure of the linear relationship between each component and the optimal linear combination of the components found by the CCA.

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