Sequential logistic models for 30 days mortality after CABG: Pre-operative, intra-operative and post-operative experience – The Israeli CABG study (ISCAB)

Three models for early mortality after CABG

Simchen Elisheva[1,2], Galai Noya[2,3], Zitser-Gurevich Yana[2], Braun Dalit[2] &
Mozes Benjamin[4] for the ISCAB Consortium*

[1]*School of Public Health, Hebrew University and Hadassah, Jerusalem;* [2]*Department for Health Services Research, Ministry of Health, Jerusalem;* [3]*Department of Epidemiology, Ben-Gurion University of the Negev, Beer-Sheva;* [4]*Unit for Quality Assurance, Gertner Institute, Shiba Hospital, Tel Aviv, Israel (Present address: Ben-Gurion University, Beer-Sheva, Israel)*

Abstract. *Objectives*: The goal of this paper was to examine the added effect of operative and post-operative variables on 30 days mortality, in addition to patients' case-mix factors. *Setting and design*: A prospective study of 4835 patients, 95% of all Israeli patients who underwent coronary artery bypass grafting (CABG) in 1994. Information related to risk of death was collected at admission to hospital (preceding the operation), at time of the operation and in the immediate post-operative period. Deaths were independently ascertained. *Method*: Data collectors followed every patient from admission to discharge. Sequential logistic models were constructed for the 'case-mix', 'operative' and the 'post-operative' periods in chronological order. Each model incorporated and adjusted for the risk estimated at the previous point in time, by forcing individual risk scores. *Results*: Significant pre-operative risk factors for 30 days mortality, in the case-mix model included mainly severity of illness characteristics, such as, left ventricular dysfunction and emergency admission, (c-statistic 78.8%). Model 2 (the 'operation' model) included in addition to the case-mix score, excessive duration of the operation per graft, bleeding, etc. (c-statistic 85.3%). The post-operative model showed the added effect of the post-operative factors such as low haemoglobin, additional surgery, and excessive time on respirator, (c-statistic 92.4%). *Conclusions*: The sequential analysis was an efficient method for updating patients' risk over time, where the number of events was small, relative to the number of risk factors. The addition of peri-operative factors increased significantly the predictive power of the model, adding clinical insights to the role of the hospital experience on 30 days mortality.

Key words: Coronary Artery Bypass, Early mortality, Sequential logistic models

Abbreviations: CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; CTN = central-team nurse; CVA = cerebro-vascular accident; DM = diabetes mellitus; EF = ejection fraction; IABP = intra-aortic balloon pump; ICCU = intensive cardiac care unit; IMA = internal mammary artery; ISCAB = Israeli study of coronary bypass grafting; LV = left ventricle; LMD = left main disease; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; SOB = shortness of breath

Introduction

Most outcome studies adjust for patient's pre-operative risk profile, which is regarded as the main determinant of mortality [1–16]. The fact that what happens after entry to hospital is not directly measured suggests an underlying assumption that quantification of risk associated with patient management is beyond the scope of observational studies. While recognising that surgical technique is hard to quantify, and meaningful data on the operation and the post-operative period hard to get, there is evidence from the literature that these factors are important. 'Process' factors like duration of the operation, the type of grafting used, re-exploration for bleeding have been shown to be associated with mortality. Similarly, in the immediate post-operative period some intra-operative complications are quoted, like inability to wean patients off respirators, need for

inotrops and blood transfusions, and development of wound infections [18–29]. We utilised the full cooperation of surgeons collaborating in Israeli study of coronary bypass grafting (ISCAB), who made available the operation reports, the post-operative daily follow-ups to model the time sequence of events that preceded death, by constructing sequential logistic models of risk, in the order in which factors affected patients' outcomes.

The goal of this paper was to examine the role of the operation and the post-operative period on the risk of dying after coronary artery bypass grafting (CABG), against the background of the pre-operative risk the patient presented on admission. The assumption was that such 'process' factors might be more amenable to intervention then case-mix factors.

Materials and methods

Eligibility for the ISCAB included every individual in the country, who underwent isolated coronary bypass during 1994. All 14 institutions performing CABG procedures (including private) participated [4]. Patients were enrolled between 1 January and 31 December 1994. Of the 5100 isolated coronary bypass operations performed during the year, 4835 patients (95%) are included in this report. The five percent missing are due to data-collectors' vacations. There was no reason to suspect a selection bias, as holidays were taken at different times during the year, and were reported and coordinated by the central office of the study, and not by hospital staff.

Standardisation of data collection

For the achievement of comparable data from the various hospitals, data collectors were especially hired and trained. These were mainly nurses from the cardiac departments or intensive cardiac care units (ICCUs), who were familiar with the kind of patients under study. A preliminary training and a pilot project preceded the initiation of the main study, when data collectors learned the study questionnaires, the importance of minimising missing data, and the use of laptop computers. Further on-site training was provided by three rotating central-team nurses (CTNs). They visited the sites unexpectedly and supervised the field nurses throughout the year. Formal standardisation of the data collection was performed by the CTNs, on a 5% sample of the patients. Duplicated questionnaires were evaluated for systematic errors, and used for further training. Details of the analysis of standardisation data were reported elsewhere [17]. The day to day operating room records were reviewed by CTNs monthly to ensure a complete coverage of eligible patients.

Sources of data included

Pre-operative patient interview; follow-up of patients from admission until discharge; operation report (filled by the surgeons); summary of the hospitalization (filled by the surgeon); catheterization report (filled by the various cardiologists and coded by one expert cardiologist); and mortality records from the Israeli population registry.

Validation of the population registry information was performed. Hospital data on known in-hospital deaths were matched with the Israeli population registry records. It was found that the latter was updated within 4–5 days after death, with 100% match with data collected by the nurse. No validation could be done on the quality of the operating room report, the hospitalization summary and the cardiac catheterization report.

Study variables

The outcome variable was defined as mortality within 30 days after the operation, regardless of hospitalization status. Explanatory variables were usually derived from more than one source (Table 1), like patient's interview, medical file, and the hospitalization summary. It was decided to use a sensitive definition of a risk factor, whereby one source was considered sufficient to identify risk.

Among patient case-mix factors, left ventricular dysfunction was used as a proxy variable for ejection fraction, because the test was not performed for the most severe cases due to clinical concern.

There were 40 patient-characteristics on admission, 17 operation variables, and 26 post-operative factors, which were screened for their univariate association with mortality.

Statistical analysis

The purpose of the analysis was to maximise the efficiency of formulating a risk statement for each patient, including his pre-, intra- and post-operative periods, utilising all available information. The analysis was planned to identify the relative contribution of each set of variables, corresponding to points in time, to the risk of death, and to help characterise individuals whose risk of mortality changed from baseline, as a result of the hospital experience. Variables were initially screened for crude association with 30 days mortality by using univariate exploratory analysis. Those associated with mortality at $p \leqslant 0.1$ were introduced into the multivariate logistic models. Patients with missing values were excluded from the analysis except for missing values exceeding 5% of the risk group. In these cases the missing were treated as a separate category and retained in the model in order to minimise the exclusion of observations with incomplete records. The variables so

Table 1. Significant univariate determinants of 30 days mortality in patients undergoing coronary artery bypass grafting, ISCAB 1994

Source of information	Variable Risk category	n[a]	Mortality rate, %	OR	p-Value
(A) Case-mix factors (n = 4835 patients)					
Preoperative interview, medical records	Age (years)				
	⩾75	579	6.6	4.8	0.009
	65–74	1963	3.5	2.5	0.120
	55–64	1468	2.2	1.5	0.479
	45–54	615	1.3	0.9	0.889
	<45	210	1.4	1.0	
Preoperative interview, medical records	Gender				
	Female	1029	5.1	2.0	<0.001
	Male	3806	2.6	1.0	
Preoperative interview	Marital status				
	No spouse	793	5.2	1.9	<0.001
	Spouse	4042	2.7	1.0	
Preoperative interview	Living status				
	Alone	481	4.8	1.8	0.009
	Not alone	4296	2.7	1.0	
Preoperative interview	Employment				
	Housewife	322	5.9	8.2	<0.001
	Retired	2507	4.0	5.4	<0.001
	Part time	346	0.6	1.0	
	Full time	1504	0.8	1.0	
Preoperative interview	Physical activity				
	No	2712	3.7	4.1	<0.001
	Yes	1970	0.9	1.0	
Preoperative interview	Hospitalization in past 2 years				
	⩾3	743	5.3	2.7	<0.001
	1–2	2662	2.7	1.3	0.217
	No	1378	2.0	1.0	
Medical records	Days in hospital prior to operation				
	0	597	3.5	1.7	0.037
	1	2201	2.0	1.0	
	2–7	1038	3.4	1.7	0.024
	⩾8	979	4.8	2.4	<0.001
Hospitalization summary, operative report	Type of surgery				
	Emergency	108	17.6	11.1	<0.001
	Urgent	1848	4.2	2.3	<0.001
	Elective	2820	1.9	1.0	
Operative report, hosp. summary	IABP[b] prior to operation				
	Yes	107	15.0	6.0	<0.001
	No	4660	2.8	1.0	
Preoperative interview, hosp. summary	Left ventricular dysfunction				
	Diuretics with SOB[b]	358	8.1	4.2	<0.001
	Diuretics w/o SOB[b]	493	5.1	2.6	<0.001
	No	3917	2.0	1.0	
Catheterization report, hosp. summary	Coronary artery disease				
	3 vessels with LM[b]	313	6.7	3.7	<0.001
	3 vessels w/o LM[b]	1845	3.7	1.9	0.010
	LM with <3 vessels	515	3.3	1.7	0.058
	<3 vessels	2084	1.9	1.0	

Table 1. (*Continued*)

Source of information	Variable Risk category	n^a	Mortality rate, %	OR	*p*-Value
Preoperative interview	Canadian Heart Association Criteria				
	Class 5	803	3.1	1.5	0.036
	Class 3–4	2107	3.1	1.5	0.101
	Class 1–2	1017	1.5	1.0	
	No angina	747	2.8	1.0	
Preoperative interview, hosp. summary	Hypercholesterolemia				
	Yes	2532	2.5	0.7	0.015
	No	2296	3.7	1.0	
Preoperative interview, hosp. summary	Peripheral vascular disease				
	Yes	447	5.8	2.2	< 0.001
	No	4311	2.8	1.0	
Operative report, hosp. summary	Calcified aorta				
	Yes	905	5.0	2.2	< 0.001
	No	3573	2.3	1.0	
Preoperative interview, hosp. summary	Cerebro-vascular event				
	CVA[b]	238	6.3	2.3	0.003
	TIA[b]	125	3.2	1.1	0.836
	No	4469	2.9	1.0	
Preoperative interview, hosp. summary	Hypertension				
	Yes	2743	3.8	1.7	0.003
	No	2092	2.5	1.0	
Preoperative interview, hosp. summary	Arrhythmia				
	Yes	669	5.0	1.9	0.001
	No	4159	2.8	1.0	
Preoperative interview, hosp. summary	Diabetes mellitus				
	Yes	1438	4.7	1.9	< 0.001
	No	3397	2.4	1.0	
Preoperative interview, hosp. summary	Chronic obstructive lung disease				
	Yes	279	5.0	1.7	0.054
	No	4551	2.9	1.0	
Hosp. summary	Chronic liver disease				
	Yes	8	37.5	19.5	< 0.001
	No	4750	3.0	1.0	
Hosp. summary	Chronic renal disease				
	Yes	174	12.1	4.9	< 0.001
	No	4584	2.7	1.0	
Medical records	Serum creatinine (mg/dl)				
	⩾1.4	482	7.5	3.0	< 0.001
	< 1.4	4353	2.6	1.0	
Hosp. summary	HCFA severity score				
	5	114	16.7	53.9	< 0.001
	4	1916	4.2	11.9	< 0.001
	3	202	8.4	24.8	< 0.001
	2	1714	1.5	3.9	0.023
	1	812	0.4	1.0	
(B) Operative factors (n = 4835 patients)					
Operative report, hosp. summary	Cross-clamp time per graft (min)				
	No cross-clamp	150	5.3	2.0	0.059
	> 25	2079	5.1	1.9	0.004
	20–25	1306	3.4	1.3	0.323
	15–19	618	1.9	1.0	
	< 15	494	2.5	1.0	

Table 1. (*Continued*)

Source of information	Variable Risk category	n[a]	Mortality rate, %	OR	*p*-Value
Operative report	Time on heart–lung machine (min)				
	No HLM[b]	62	4.8	3.4	0.049
	> 180	246	11.8	8.9	< 0.001
	151–180	235	5.5	3.9	< 0.001
	91–150	1940	2.7	1.8	0.007
	⩽ 90	2157	1.5	1.0	
Operative report, hosp. summary	Withdrawal from heart–lung machine				
	No HLM[b]	72	11.1	7.9	< 0.001
	⩾ 2 attempts	160	18.1	13.9	< 0.001
	1st attempt w/inotrops	744	5.7	3.8	< 0.001
	1st attempt w/o inotrops	3590	1.6	1.0	
Operative report	Type of cardioplegia				
	Both	61	9.8	3.9	0.002
	Blood	2787	2.8	1.0	
	Crystalloid	953	2.3	1.0	
	No cardioplegia	836	2.9	1.0	
Operative report, hosp. summary	Intra-operative IABP[b]				
	Yes	112	32.1	19.6	< 0.001
	No	4653	2.4	1.0	
Operative report	Blood transfusions				
	⩾ 3 portions	230	10.9	5.8	< 0.001
	2 portions	533	3.8	1.8	0.018
	0–1 portions	3329	2.1	1.0	
Operative report, hosp. summary	Type of graft				
	Exclusive vein	351	6.8	2.4	< 0.001
	Both vein + IMA[b]	4126	2.9	1.0	
	Exclusive IMA[b]	288	1.0	0.3	0.075
Operative report	Source of vein graft				
	Thigh only	687	3.9	1.8	0.017
	Both thigh + calf	2124	3.8	1.8	0.004
	Calf only	1667	2.2	1.0	
	No venous graft	288	1.0	–	
Operative report, hosp. summary	Number of bypasses				
	⩾ 4	1878	3.7	1.4	0.050
	2–3	2672	2.7	1.0	
	1	221	1.8	0.6	0.420
Operative report, hosp. summary	Incomplete revascularization				
	Yes	1016	5.0	1.9	< 0.001
	No	3687	2.6	1.0	
Operative report, hosp. summary	Complicated surgery[c]				
	Severe	285	17.2	9.4	< 0.001
	Moderate	107	4.7	2.2	0.089
	No	4443	2.2	1.0	
(C) Post-operative factors (n = 4805 patients)					
Daily follow-up	Blood pressure decline				
	Yes	1314	7.0	8.9	< 0.001
	No	3491	1.0	1.0	
Daily follow-up, hosp. summary	Arrhythmia				
	Vent. fibrillation[b]	76	25.0	39.7	< 0.001
	Vent. tachycardia	119	7.6	9.7	< 0.001
	Atrial tachycardia	2085	3.4	4.2	< 0.001
	None	2525	0.8	1.0	

Table 1. (*Continued*)

Source of information	Variable Risk category	n^a	Mortality rate, %	OR	p-Value
Daily follow-up, hosp. summary	Acute myocardial infarction				
	Yes	53	13.2	7.8	<0.001
	Probable	163	7.4	4.1	<0.001
	No	4589	2.2	1.0	
Daily follow-up	Getting steroids				
	Yes	865	6.2	3.9	<0.001
	No	3940	1.7	1.0	
Daily follow-up, hosp. summary	Heart failure				
	Yes	99	25.2	16.4	<0.001
	No	4706	2.0	1.0	
Daily follow-up	Stroke				
	Yes	125	19.2	11.3	<0.001
	No	4680	2.0	1.0	
Daily follow-up	Haemoglobin (mmol/l)				
	<8	316	10.1	5.6	<0.001
	⩾8	4489	1.9	1.0	
Daily follow-up	On respirator (hours)				
	>24	508	15.7	19.9	<0.001
	⩽24	4297	0.9	1.0	
Daily follow-up, hosp. summary	Wound infection				
	Mediastinitis/sepsis	138	21.0	12.2	<0.001
	Chest wound infection	251	1.6	0.7	0.190
	Leg wound infection	182	3.8	1.8	0.564
	Discharge (probable inf.)	1148	1.2	0.5	0.001
	None	3086	2.1	1.0	
Daily follow-up, hosp. summary	Gastro-intestinal bleeding				
	Yes	129	10.1	5.0	<0.001
	No	4665	2.2	1.0	
Daily follow-up	Blood transfusions				
	⩾5 portions	592	10.5	8.4	<0.001
	<5 portions	4213	1.4	1.0	
Daily follow-up, hosp. summary	Additional surgery				
	Yes	216	19.4	13.9	<0.001
	No	4589	1.7	1.0	
Daily follow-up	Urine volume (ml)				
	<1000	288	14.2	9.3	<0.001
	⩾1000	4517	1.7	1.0	

[a] Missing values are not presented in the table.
[b] PTCA – percutaneous transluminal coronary angioplasty; IABP – intra-aortic balloon pump; SOB – shortness of breath; CVA – cerebrovascular accident; TIA – transient ischemic attack; LM – left main; HLM – heart–lung machine; Vent. – Ventricular.
[c] Definition based on specific diagnoses, as massive bleeding re-do bypasses, etc.

treated were left ventricular dysfunction, cross-clamp time per graft and withdrawal from heart–lung machine.

The sequential logistic models were constructed so that each one added a new group of variables relating to a different time point in the patient's hospitalization course. The original study group included 4835 patients of which 150 died within 30 days of the operation. The first model included 4738 patients with 147 deaths who had a complete data set on patient inherent characteristics at entry to hospital.

Model 1 ('case-mix' model)

$$\text{logit}(\text{prob}\{Y_i = 1 | X_i^c\}) = \beta_0 + \sum_j \beta_j X_{ij}^c$$

where Y_i is the indicator for death for individual i and $\mathbf{X}_i^c = (X_{i1}^c, \ldots, X_{ij}^c)$ are patient inherent characteristics as he entered the hospital. For each

individual we calculated a risk score based on model 1, defined as:

$$S_{1i} = \hat{\beta}_0 + \sum_j \hat{\beta}_j X_{ij}^c$$

where $\hat{\beta}_j$ are the estimated coefficients.

In the next step we built a 2nd multivariate logistic model, which included the patient risk score from the 1st model and a new set of intra-operative factors (the 'operation' model). For this model data were available on 4673 patients including 144 death events (excluding 62 of those alive and 3 of the dead due to missing data).

Model 2 ('operative model')

$$\text{logit}\big(\text{prob}\{Y_i = 1 | S_{1i}, \mathbf{X}_i^0\}\big) = \gamma_0 + \gamma S_{1i} + \sum_k \gamma_k X_{ik}^0$$

where $\mathbf{X}_i^0 = \left(X_{i1}^0, \ldots, X_{ik}^0\right)$ are the operative factors. For each individual we calculated a risk score based on Model 2 defined as:

$$S_{2i} = \hat{\gamma}_0 + \hat{\gamma} S_{1i} + \sum_k \hat{\gamma}_k X_{ik}^0$$

where $\hat{\gamma}_k$ are the estimated coefficients.

The same process was applied once more to form the 3rd model, which included the combined score from model 2 and the factors depicting the post-operative complications (the 'post-operative' model). For this model 29 patients who died within the first 24 hours of the operation were a-priori excluded (one additional death within 24 hours dropped from model 2 due to missing data). Complete data were available on 4644 patients with 115 death events.

Model 3 ('post operative model')

$$\text{logit}(\text{prob}\{Y_i = 1 | S_{2i}, \mathbf{X}_i^p\}) = \delta_0 + \delta S_{2i} + \sum_m \delta_m X_{im}^p$$

where $\mathbf{X}_i^p = (X_{i1}^p, \ldots, X_{im}^p)$ are the post-operative factors. For each individual we calculated a risk score based on model 3 defined as:

$$S_{3i} = \hat{\delta}_0 + \hat{\delta} S_{2i} + \sum_m \hat{\delta}_m X_{im}^p$$

where $\hat{\delta}_m$ are the estimated coefficients.

A possible bias due to the use of summary scores in the sequential modelling rather then the creating of a one-time model was examined. The one-time models, one for case-mix and operative factors, and one for all study variables were constructed and compared with the sequential models (Appendices 1, 2).

The final model was validated by performing the sequential modeling process on a random half of the study group (learning set) and applying the resulting model to predict mortality in the other half (test set). That is, the β coefficients in the final models (1–3) were re-estimated using only observations in the learning set and these results were applied to predict

mortality in the test set. Comparison of expected to observed mortality rates was done, for each stage (case-mix, operative, post-operative), with a χ^2 test. These comparisons were applied for the overall test group as well as by quintiles of expected risk.

Results

Four thousand eight hundred and thirty five patients completed their follow-up and were entered into the analysis. Of them 150 patients died until 30 days after the operation, yielding a crude mortality rate of 3.1%.

Variables that were screened and had a significant association with mortality up to 30 days, are presented in Table 1. The table is divided into (A) patient-characteristics, (B) the operative factors, and (C) the post-operative factors. Odds ratios (OR) for each of the factors were calculated using the lowest category of risk as the reference. *p*-Values were

Table 2. Model 1. Patient case-mix risk factors: Multivariate model for 30 days mortality after CABG. ISCAB 1994

Risk factors Risk category	OR	*p*-Value
Type of surgery		
Emergency	9.79	< 0.001
Urgent	2.02	< 0.001
Elective	1.00	
Left ventricular dysfunction[a]		
Diuretics w/shortness of breath	2.69	< 0.001
Diuretics w/o shortness of breath	2.24	< 0.001
No	1.00	
Creatinine (mg/dl)		
⩾1.4	2.28	< 0.001
< 1.4	1.00	
Coronary artery disease[b]		
3 vessels with left main stenosis	2.29	0.005
3 vessels only	1.78	0.005
Left main with < 3 vessels	1.25	0.473
< 3 vessels	1.00	
Age		
> 75	2.00	0.002
70–75	1.58	0.027
< 70	1.00	
Diabetes mellitus		
Yes	1.97	< 0.001
No	1.00	
Sex		
Female	1.56	0.020
Male	1.00	
Goodness-of-fit	c-statistic = 0.788	

[a] The model also included a category for missing values of left ventricular dysfunction, which was significantly associated with mortality.
[b] Coronary artery stenosis > 70%; left main stenosis > 50%.

obtained by univariate logistic models. Missing values were not included in the table.

Variables, present on admission, that had a significant association with mortality at $p < 0.1$ were introduced into the 1st model ('case-mix' model) and the model was reduced with a backward elimination process. Factors that maintained an independent association with mortality, at $p \leqslant 0.05$, within the model were all related to the extent of the coronary disease, the function of the left ventricle (LV) and the patient's general clinical condition (Table 2). The model included: emergency operation (OR: 9.79; $p < 0.001$); left ventricular dysfunction (OR: 2.69; $p < 0.001$); 3 vessels disease with or without left main disease (LMD) (OR: 2.29; $p = 0.005$); blood creatinine level > 1.4 mg/dL (OR: 2.28; $p < 0.001$); old age (OR: 2.00; $p = 0.002$); female gender (OR: 1.56; $p = 0.02$); and a diagnosis of Diabetes Mellitus (DM) (OR: 1.97; $p < 0.001$). The c-statistic of this model was 78.8%.

Patients' scores, based on the β coefficients of this model, were then entered into the 2nd model ('operative'), together with added operative risk factors. Model 2 included: score from model 1 (OR per unit of score: 2.36; $p < 0.001$); need for intra-operative balloon pump (IABP); operative complications (such as intra-operative difficulty to control bleeding, or, more bypasses then were originally planned); prolonged cross-clamp time (over 25 min per graft),

and difficulty in withdrawing a patient from the heart–lung machine (use of inotrops or, repeated attempts). The c-statistic for this model was 85.3% (Table 3).

Risk scores derived from this model, now including both patient and operative characteristics, had a strong association with mortality when entered into model 3 (OR per unit of score: 1.7; $p < 0.001$). Additional post-operative complications included: low haemoglobin, stroke, heart failure, blood pressure decline, steroid treatment, need for five or more blood transfusions, and additional surgery. The c-statistic was 92.5% (Table 4).

The simultaneous model using all study variables for the operative and post-operative periods were compared with our sequential method in Appendices 1, 2. The tables demonstrate the similarity of the β-coefficients and the p values, at each stage with either method.

Figure 1 represents the distribution of the risk scores for all patients, derived from each of the se-

Table 3. Model 2. Procedural risk factors adjusted for case-mix score: Multivariate model for 30 days mortality after CABG. ISCAB 1994

Risk factors Risk category	OR	p-Value
Case mix severity score		
(per 1 unit)	2.36	< 0.001
Intra-operative intra-aortic balloon pump		
Yes	4.47	< 0.001
No	1.00	
Complicated surgery[a]		
Severe	4.12	< 0.001
Moderate	1.50	0.424
No	1.00	
Cross-clamp time (per graft)[b]		
No cross-clamp	2.66	0.016
> 25 min	1.59	0.078
≤ 25 min	1.00	
Withdrawal from heart–lung machine[b]		
≥ 2 attempts	2.24	0.016
1 attempt w/inotrops	1.69	0.019
1 attempt w/o inotrops	1.00	
Goodness-of-fit	c-statistic = 0.853	

[a] Definition based on specific diagnoses, such as, massive bleeding, added bypasses etc.
[b] The model also included categories for missing values of cross-clamp time and withdrawal from heart–lung machine, which were significantly associated with mortality.

Table 4. Model 3. Post-operative factors adjusted for combined score: Multivariate model for 30 days mortality after CABG, ISCAB 1994

Risk factors Risk category	OR	p-Value
Combined severity score[a]		
(per 1 unit)	1.70	< 0.001
Haemoglobin (mmol/l)		
< 8	6.85	< 0.001
≥ 8	1.00	
Stroke		
Yes	6.07	< 0.001
No	1.00	
Heart failure		
Yes	5.40	< 0.001
No	1.00	
Urine volume (ml)		
< 1000	5.02	< 0.001
≥ 1000	1.00	
Getting steroids		
Yes	2.59	< 0.001
No	1.00	
Blood pressure decline		
Yes	2.56	< 0.001
No	1.00	
Additional surgery during current admission		
Yes	2.62	0.001
No	1.00	
Ventricular dysrhythmia		
Yes	2.21	0.016
No	1.00	
Transfusions (blood or products)		
≥ 5 portions	2.09	0.005
< 5 portions	1.00	
Goodness-of-fit	c-statistic = 0.925	

[a] Based on Models 1&2.
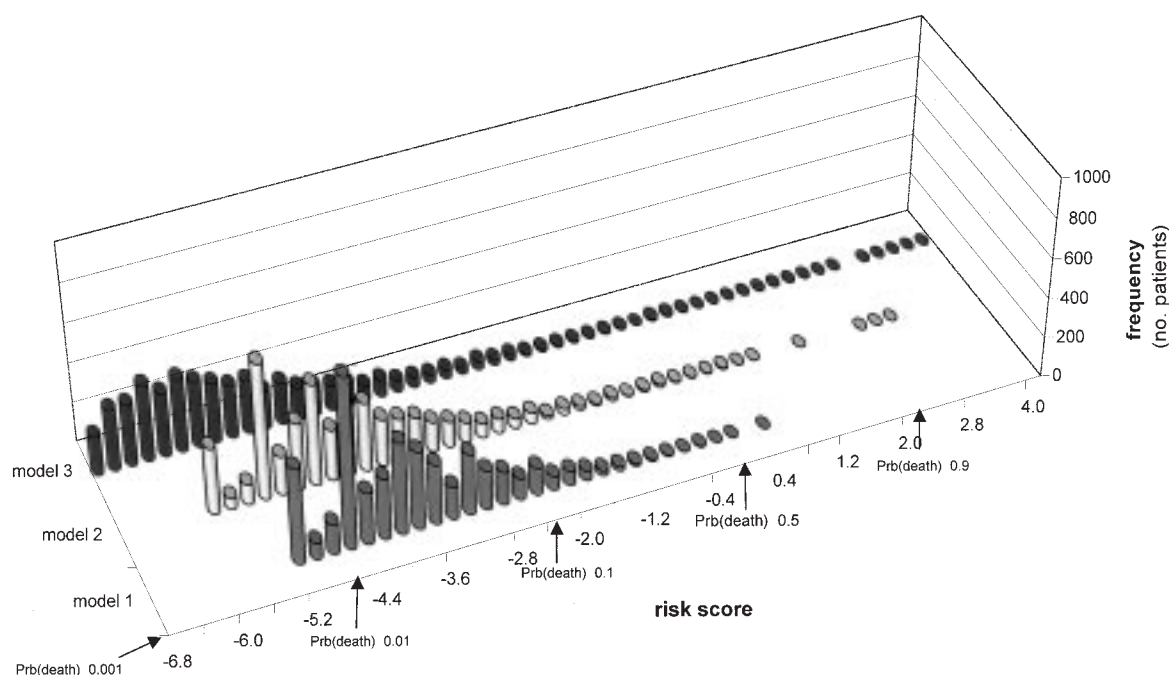
Figure 1. Distribution of risk scores derived from the sequential models (n = 4644 with 115 deaths). Model 1 – case-mix factors; Model 2 – adding operative factors; Model 3 – adding post-operative factors.

quential models. 'Case-mix' model scores vary from −5.2 to 0.4, while subsequent distributions (from models 2 and 3) show a wider spread: from −5.6 to 2.7 and from −6.8 to 4.00, respectively.

The cross-validation results, comparing the expected to observed 30 days mortality rates in the test set indicated an excellent correspondence: model 1 – 3.05 vs. 3.16%; model 2 – 2.95 vs. 3.17%; and model 3 – 2.64 vs. 2.46% for expected and observed mortality rates respectively. These differences were not statistically significant. Validation was also carried out considering quintiles of risk for each model and differences between observed and expected remained not significant.

Discussion

This analysis is from an observational multi-center prospective study that followed surgical patients at sequential points in time, from entry to hospital until discharge. We attempted to follow the chronological order in which factors had affected 30 days deaths, by constructing sequential models including first patients' characteristics as they entered the hospital, then adding their experience there, i.e. the operative and the post-operative period.

Most studies in the literature infer that residual variability in mortality after adjusting for case-mix factors is the result of differences in patient care [1, 2, 6]. In the present analysis there was interest in explicitly modelling the 'process' of care, while adjusting for patient characteristics. In spite of the adjustments made for 'case-mix' factors, there was a

strong independent effect of intra-operative and post-operative factors on the risk of dying. Our sequential modelling suggests strongly that not all complications during the operation and in the post-operative period could be attributed to patient inherent risk at the time of surgery. The c-statistic of the models incorporating these additional factors rose from 78.8 to 92.5%. This suggested an increase in the discriminatory power of the models, resulting in a more accurate estimate of risk to individual patients. Figure 1 demonstrates the change in the distribution of individual risk scores as the analysis moved from Models 1 to 3. The range of risk scores increased in both directions, i.e. patients who did not have additional risk factors during the hospitalisation were shifted towards lower risk scores while those with added risks increased their score. The meaning of this in the clinical reality of a cardiac surgery ward is that using case-mix factors alone for estimating risk of 30 days mortality tends to overestimate the risk for patients who will not have a complicated surgery, and underestimate the risk of those who will.

One of the advantages of the sequential method over a simultaneous modelling of all risk factors was the non-biased risk estimates. This is because at each point in time the model could use the 'true' population at risk. For example, if we used a one-time model of all study variables we would have to exclude all those who died within 24 hours of the operation because they had no post-operative follow-up. In our study this would have meant the exclusion of 20% of all deaths. The sequential method avoided this problem using the risk scores. Thus, although the post-operative model included only survivors of the first 24 hours, their pre-

and intra-operative risk estimates were based on the original cohort that entered the operating theatre.

Another advantage of the scoring system is its efficiency in studies where the number of events is small (mortality rate 3%) relative to the number of possible risk factors. However, a possible limitation of using the scores is, that it does not allow the observation of reflected effects of the specific factors composing the scores.

In general, our models fit well with other published reports [4, 6–15]. Old age, female gender, emergency operation, and poor LV function were the main determinants of early mortality. Some, [11–15] like us, included in addition, three vessels disease, LMD involvement, and co-morbid states such as diabetes and renal dysfunction. The only study we could find [25] that modelled the operation cited prolonged aortic cross-clamp time, absence of cold-blood cardioplegia and non-use of bilateral internal mammary artery (IMA) as predictors of operative mortality. In addition, re-do surgery, intra-operative bleeding, intra-operative transfusions, intra-operative intra-aortic balloon pump (IABP), number of grafts per patient, exclusive venous grafting, incomplete revascularization, are usually cited as operative determinants of

mortality in trials on different operative techniques and observational studies of the operating room [20, 22–28]. Conceptually, the immediate post-operative period usually is difficult to model, probably because factors in this period are of a mixed kind. Some are intermediate outcomes (post-operative myocardial infarction (MI), stroke, renal malfunction), others were initiated in the operating theatre, and only became evident in the post-operative period. Similar to our findings, a Swedish study [29] depicted neurological complications, the use of circulatory assist devices, re-operation and ventilator more than 24 hours as independent predictors of 30 days mortality.

The cross-validation process was adapted to the sequential modeling approach and implied validation of three related models. The results showing a good agreement in all stages lends further confidence in the predictive ability of the model.

In conclusion, the sequential model approach was efficient in explicitly examining the effect of new additional factors on existing risk. It helped clarify and quantify the sequence of events that affected the risk of 30 days deaths after CABG, using true population at risk for each stage of the analysis.

Appendix 1. Comparing the β-coefficients and p-values of two logistic models: Simultaneous Model 2 (case-mix and operative factors) and a model containing a summary score for the case-mix factors, ISCAB 1994

Risk factors Risk category	Model 2: full		Model 2: score	
	β-Coeff.	p-Value	β-Coeff.	p-Value
Intercept	−5.379	< 0.001	−1.233	< 0.001
Type of surgery				
Emergency	0.373	0.069		
Urgent	1.806	< 0.001		
LVD[a]				
Diuretics w/SOB[b]	0.952	< 0.001		
Diuretics w/o SOB[b]	0.711	0.004		
Serum creatinine (mg/dl)				
⩾ 1.4	0.732	0.002	⇒ Score	
Coronary artery disease				
3 vessels with LM[b]	0.646	0.047	0.859	< 0.001
3 vessels only	0.460	0.038		
LM[b] with < 3 vessels	0.206	0.520		
Age (years)				
> 75	0.815	< 0.001		
70–75	0.417	0.065		
Diabetes mellitus				
Yes	0.602	0.002		
Gender				
Female	0.549	0.007		
Intra-operative IABP[b]				
Yes	1.561	< 0.001	1.498	< 0.001
Complicated surgery				
Severe	1.431	< 0.001	1.415	< 0.001
Moderate	0.425	0.410	0.405	0.420
Cross-clamp time[a]				
No cross-clamp	0.981	0.017	0.978	0.016
> 25 min per graft	0.452	0.086	0.462	0.078

Appendix 1. (*Continued*)

Risk factors Risk category	Model 2: full		Model 2: score	
	β-Coeff.	*p*-Value	β-Coeff.	*p*-Value
Withdrawal from heart–lung machine[a]				
⩾2 attempts	0.845	0.012	0.808	0.016
1 attempt w/inotrops	0.525	0.020	0.524	0.019
Goodness-of-fit	c-statistic 0.85		0.85	

[a] The model also included categories for missing values of LVD, cross-clamp time, withdrawal from heart–lung machine which were significantly associated with mortality.
[b] LVD – Left ventricular dysfunction; SOB – shortness of breath; LM – left main; IABP – intra-aortic balloon pump.

Appendix 2. Comparing the *β*-coefficients and *p*-values of two logistic Models: simultaneous model 3 with all study variables and a model containing the summary score, ISCAB 1994

Risk factors Risk category	Model 3: full		Model 3: score	
	β-Coeff.	*p*-Value	β-Coeff.	*p*-Value
Intercept	−7.366	< 0.001	−3.753	< 0.001
Type of surgery				
Emergency	0.851	0.120		
Urgent	0.034	0.890		
LVD[a]				
Diuretics w/SOB[b]	0.955	0.004		
Diuretics w/o SOB[b]	0.494	0.110		
Serum creatinine (mg/dl)				
⩾1.4	0.752	0.010		
Coronary artery disease				
3 vessels with LM[b]	0.495	0.240		
3 vessels only	0.378	0.170		
LM with < 3 vessels	−0.094	0.830		
Age				
> 75	0.893	0.004	⇒ Score	
70–75	0.405	0.170	0.528	< 0.001
Diabetes mellitus				
Yes	0.972	< 0.001		
Gender				
Female	0.418	0.120		
Intra-operative IABP[b]				
Yes	0.505	0.250		
Complicated surgery				
Severe	0.534	0.120		
Moderate	0.085	0.890		
Cross-clamp time[a]				
No cross-clamp	1.104	0.060		
> 25 min per graft	0.353	0.290		
Withdrawal from heart-lung machine[a]				
⩾2 attempts	0.563	0.180		
1 attempt w/inotrops	−0.188	0.530		
Hemoglobin (mmol/l)				
< 8	1.651	< 0.001	1.610	< 0.001
Stroke				
Yes	1.823	< 0.001	1.795	< 0.001
Heart failure				
Yes	1.815	< 0.001	1.777	< 0.001
Urine volume (ml)				
< 1000	1.549	< 0.001	1.562	< 0.001
Getting steroids				
Yes	1.059	< 0.001	0.933	< 0.001

Appendix 2. (*Continued*)

Risk factors Risk category	Model 3: full		Model 3: score	
	β-Coeff.	*p*-Value	β-Coeff.	*p*-Value
Blood pressure decline				
Yes	1.076	< 0.001	1.001	< 0.001
Additional surgery				
Yes	0.905	0.004	0.862	0.005
Ventricular dysrhythmia				
Yes	1.027	0.003	1.336	0.002
Transfusions (blood or products)				
⩾ 5 portions	0.774	0.005	0.794	0.003
Goodness-of-fit c-statistic	0.93		0.93	

[a] The model also included categories for missing values of LVD, cross-clamp time, withdrawal from heart–lung machine which were significantly associated with mortality.

[b] LVD – left ventricular dysfunction; SOB – shortness of breath; LM – left main; IABP – intra-aortic balloon pump.

References

1. Hannan EL, Kilburn H, Racz M, et al. Improving the outcomes of coronary artery bypass surgery in New York State. JAMA 1994; 271: 761–766.
2. O'Connor GT, Plume ST, Olmstead EM, et al. A regional intervention to improve the hospital mortality associated with coronary artery bypass graft surgery. JAMA 1996; 275: 841–848.
3. Luft HS, Romano PS. Chance, continuity, and change in hospital mortality rates coronary artery bypass graft patients in California hospitals, 1983 to 1989. JAMA 1993; 270: 331–337.
4. Mozes B, Olmer L, Galai N, Simchen E, for the ISCAB Consortium. A national study of post-operative mortality associated with coronary bypass grafting in Israel. ISCAB Consortium. Ann Thorac Surg 1998; 66(4): 1254–1262.
5. O'Connor GT, Morton JR, Diehl MJ, et al. Differences between men and women in hospital mortality associated with coronary artery bypass graft surgery. Circulation 1993; 88(Part 1): 2104–2110.
6. Tu JV, Jaglal SB, Naylor CD, et al. Multicenter validation of a risk index for mortality, intensive care unit stay, and overall hospital length of stay after cardiac surgery. Circulation 1995; 91: 677–684.
7. O'Connor GT, Plume SK, Olmstead EM, et al. A regional prospective study of in-hospital mortality associated with coronary artery bypass grafting. JAMA 1991; 266: 803–809.
8. Williams SV, Nash DB, Goldfarb N. Differences in mortality from coronary artery bypass graft surgery at five teaching hospitals. JAMA 1991; 266: 810–815.
9. Higgins TL, Estafanous FG, Loop FD, et al. Stratification of morbidity and mortality outcome by pre-operative risk factors in coronary artery bypass patient. A clinical severity score. JAMA 1992; 267: 2344–2348.
10. Grover FL, Johnson RR, Marshall G, et al. Factors predictive of operative mortality among coronary artery bypass subsets. Ann Thorac Surg 1993; 56: 1296–1307.
11. Wright JG, Pifarre R, Sullivan HJ, et al. Multivariate discriminant analysis of risk factors for operative mortality following isolated coronary artery bypass graft Loyola University Medical Centre experience, 1970 to 1984. Chest 1987; 91: 394–399.
12. Hannan EL, Kilburn H, O'Donnell JF, et al. Adult open-heart surgery in New York State. An analysis of risk factors and hospital mortality rates. JAMA 1990; 264: 2768–2774.
13. Weintraub WS, Wenger NK, Jones EL, et al. Changing clinical characteristics of coronary surgery patients. Difference between men and women. Circulation 1993; 88(5 Pt 2): II79–II86.
14. Edwards FH, Clark RE, Schwartz M. Coronary artery bypass grafting: The society of thoracic surgeons National database experience. Ann Thorac Surg 1994; 57: 12–19.
15. Parsonnet V, Dean D, Bernstein AD. A method of uniform stratification of risk for evaluating the results of surgery in acquired adult heart disease. Circulation 1989; 79(Suppl I): I3–I12.
16. Iyer VS, Russell WJ, Leppard P, et al. Mortality and myocardial infarction after coronary artery surgery. A review of 12,003 Patients. Med J Aust 1993; 159: 166–170.
17. Simchen E, Wax Y, Pevsner B. The Israeli study of surgical infections (ISSI): Methods for developing a standardised surveillance system for a multicenter study of surgical infections. Infec Control 1988; 9: 232–240.
18. He GW, Acuff TE, Ryan WH, et al. Determinants of operative mortality in elderly patients undergoing coronary artery bypass grafting. Emphasis on the influence of internal mammary artery grafting on mortality and morbidity. J Thorac Cardiovasc Surg 1994; 108: 73–81.
19. Kirklin JW, Naftel DC, Blackstone EH, et al. Summary of a consensus concerning death and ischemic events after coronary artery bypass grafting. Circulation 1989; 79(Suppl I): I81–I91.
20. Simchen E, Israeli A, Merin G, et al. Israeli women were at a higher risk than men for mortality following coronary bypass surgery. Eur J Epid 1997; 13: 503–509.

21. Rahimtoola SH, Fessler CL, Grunkemeier GL, et al. Survival 15 to 20 years after CABG for angina. J Am Coll Cardiol 1993; 21(1): 151–157.
22. Sergeant P, Lesaffre E, Flameng W, et al. Internal mammary artery: method of use and their effect on survival. Eur J Cardiothorac Surg 1990; 4: 72–78.
23. Ramstrom J, Lund O, Cadavid E, et al. Multiarterial coronary artery bypass grafting with special reference to small vessel disease and results in women. Eur Heart J 1993; 14: 634–639.
24. Utley JR, Wilde EF, Leyland SA, et al. Intraoperative blood transfusion is a major risk factor for coronary artery bypass grafting in women. Ann Thorac Surg 1995; 60: 570–575.
25. Louagie Y, Buche M, Jamart J, et al. Operative risk assessment in coronary artery bypass surgery, 1990–1993: Evaluation of perioperative variables. Thorac Cardiovasc Surg 1995; 43: 134–141.
26. Loop FD, Lytle BW, Cosgrove DM, et al. Influence of the internal mammary artery graft on 10-year survival and other cardiac events. N Engl J Med 1986; 314(1): 1–6.
27. Magovern JA, Sakert TS, Benckart DH, et al. A model for predicting transfusion after CABG. Ann Thorac Surg 1996; 61: 27–32.
28. Moulton MJ, Creswell LL, Mackey ME, et al. Reexploration for bleeding is a risk factor for adverse outcomes after cardiac operations. J Thorac Cardiovasc Surg 1996; 111(5): 1037–1046.
29. Brandrup-Wognsen G, Haglid M, Karlsson T, et al. Mortality during the two years after coronary artery bypass grafting in relation to perioperative factors and urgency of operation. Eur J Cardio-thorac Surg 1995; 9: 685–691.

Address for correspondence: Prof. E. Simchen, School of Public Health, Hadassah University Hospital, P.O. Box 12272, Ein Kerem, Jerusalem 91120, Israel
Phone: (972) 2 643 6180; Fax: (972) 2 568 1326
E-mail: esimchen@vms.huji.ac.il