UNIVERSITE DE LAUSANNE - FACULTE DE BIOLOGIE ET DE MEDECINE

Département de Médecine
Service des maladies infectieuses

Twenty-eight days and long term survival after severe sepsis and septic shock in adults

THESE

préparée sous la direction du Professeur titulaire Jean-Daniel Baumgartner, Médecin adjoint de la division des maladies infectieuses, CHUV et Médecin chef du département de médecine, Ensemble Hospitalier de la Côte, Morges

et présentée à la Faculté de biologie et de médecine de l'Université de Lausanne pour l'obtention du grade de

DOCTEUR EN MEDECINE

par

Peter TOMASI

Médecin diplômé de la Confédération Suisse

Originaire de Goldingen (SG)

Lausanne

2009

UNIL | Université de Lausanne
Faculté de biologie
et de médecine

Ecole Doctorale
Doctorat en médecine

Imprimatur

Vu le rapport présenté par le jury d'examen, composé de

Directeur de thèse	*Monsieur le Professeur titulaire* ***Jean-Daniel Baumgartner***
Co-Directeur de thèse	
Expert	*Monsieur le Professeur associé* ***Pascal Meylan***
Directrice de l'Ecole doctorale	*Madame le Professeur* ***Stephanie Clarke***

la Commission MD de l'Ecole doctorale autorise l'impression de la thèse de

Monsieur Peter Tomasi

intitulée

Twenty-eight days and long term survival after severe sepsis and septic shock in adults

Lausanne, le 27 octobre 2009

pour Le Doyen
de la Faculté de Biologie et de Médecine

Madame le Professeur Stephanie Clarke
Directrice de l'Ecole doctorale

Résumé

Nous avons effectué une étude de cohorte examinant la survie de tous les patients qui ont présenté une sepsis sévère ou un choc septique aux soins intensifs de médecine et de chirurgie du CHUV durant une période de 3 ans.

Introduction: La sepsis sévère et le choc septique constituent la deuxième cause de mortalité dans les unités de soins intensifs non coronaires. La survie à long terme est mal connue. Nous avons comparé la survie à 28 jours de notre collectif avec les données de la littérature, examiné la survie à long terme des patients ayant survécus plus de 28 jours et identifié des paramètres prédictifs de la survie.

Matériel et méthode : Nous avons classifié les patients ayant présenté un épisode septique rétrospectivement en sepsis sévère ou choc septique selon les critères de Bone (1). Les données cliniques et paracliniques ont été relevées au moment de l'épisode. Des courbes de survie uni- et multivariées ont été établies à 28 jours et à long terme chez ceux qui ont survécus plus de 28 jours, d'après les données de questionnaires envoyés aux médecins traitants.

Résultats : Durant la période de l'étude, 339 patients ont présenté un choc septique (169) ou une sepsis sévère (170). La mortalité à 28 jours a été de 33% (choc septique: 55%, sepsis sévère: 11.2%, $p<10^{-5}$). Les données significativement associées à la mortalité à 28 jours dans l'analyse de régression multivariée selon Cox ont été le type d'épisode septique (choc septique vs. sepsis sévère, p=0.001), le «Acute Physiology Score» du score APACHE II (p=0.02) et le nombre de dysfonctions d'organes (plus de trois dysfonctions, p=0.04).

227 patients ont survécu plus de 28 jours et des données de suivi ont été obtenues chez 225. Le suivi moyen après 28 jours a été de 25.1 mois (5700 mois-patients). La mortalité globale de ces patients, extrapolée des courbes de Kaplan-Meyer, a été de l'ordre de 7% à 1 an et de 15% à 2 ans. Les données significativement associées à leur survie à long terme ont été les «chronic health points» du score APACHE II (p=0.02), l'âge (p=0.05) et le fait d'avoir subi une opération chirurgicale avant l'épisode septique (p=0.02).

Conclusion : La mortalité à 28 jours de notre cohorte de patients s'est révélée comparable aux chiffres publiés. La survie à long terme des patients ayant survécu plus de 28 jours a été satisfaisante. Elle s'est révélée indépendante de la sévérité de l'épisode septique, mais dépendait plutôt des conditions de santé sous-jacentes.

Introduction

Severe sepsis and septic shock account for 11% of admissions into intensive care units. Each year, more than 750'000 cases have been estimated to occur in the United States and the incidence is projected to increase by 1.5% per year (2). In-hospital mortality of patients with severe sepsis remains near 30% (2, 3, 4, 5) and increases to more than 60% in case of shock, despite advances in the management of critically ill patients (4, 6, 7). Severe sepsis and septic shock remain the second cause of mortality in non-coronary intensive care units (ICU) (3, 8).

Since sepsis is an acute disease, most studies have used an end-point of 28 days for assessing mortality. When the present study was undertaken, the long-term survival of patients surviving the episode of severe sepsis or septic shock was largely unknown. The knowledge of long term survival was lacking to assess the cost-benefit of investigational therapeutic interventions. Since then, a few studies have followed patients beyond 28 days (4, 5, 7, 9).

This study had two main purposes: first, to compare 28 days mortality rates observed in our hospital with rates from similar cases published in the literature; second, to assess the long term survival of patients who survived more than 28 days. A secondary purpose was to identify clinical or laboratory predictors for 28 day survival and long term survival.

The first part of the study was a retrospective analysis during a three-year period of all patients of the adult medical and surgical intensive care units (ICU) of the CHUV (Centre Hospitalier Universitaire Vaudois) in Lausanne, Switzerland. Patients who met the criteria of severe sepsis or septic shock (1) during their stay in the ICU were enrolled in our study. Data was collected from their medical files and mortality was analyzed. The second part of the study was an assessment of duration and quality of survival by mean of a questionnaire sent to the physicians in charge of the patients after discharge from the hospital or by mean of a telephone call to the patients themselves when no answer from the physician could be obtained.

Material and methods

Patient selection

The entry registries of the ICU units and the VESKA diagnostic code listings of all patients admitted to the adult medical and surgical intensive care units (ICU) of the CHUV between 1.1.1990 and 31.12.1992 were both reviewed. The entry registries are books where the main diagnoses leading to ICU admission are

reported manually for each patient. The VESKA coding system was used at the time of the study in Swiss hospitals for coding medical diagnosis and procedures for statistic purposes before the implementation of the ICD coding system (10).

The medical files of all patients with any diagnosis suggesting sepsis or infection were then carefully screened for episodes of severe sepsis or septic shock using the criteria defined by Bone RC et al (1).

Definitions

Sepsis is defined as the systemic response to infection manifested by two or more of the following conditions as a result of infection: temperature >38°C or <36°C, heart rate >90/min, respiratory rate >20/min or PaCO2 <32mmHg, WBC > 12'000 or <4000 cells/mm^3 or > 10% immature (band) forms.

Severe sepsis is defined as sepsis associated with organ dysfunction, hypoperfusion, or hypotension. Hypoperfusion and perfusion abnormalities may include, but are not limited to lactic acidosis, oliguria, or an acute alteration in mental status.

Septic shock is defined as sepsis with hypotension, despite adequate fluid resuscitation, along with the presence of perfusion abnormalities that may include, but are not limited to lactic acidosis, oliguria, or an acute alteration in mental status. Hypotension is a systolic BP of <90 mmHg or a reduction of >40 mmHg from baseline in the absence of other causes for hypotension. Patients on inotropic or vasopressor agents may not be hypotensive at the time of perfusion abnormalities.

Organ dysfunctions and perfusion abnormalities are defined as follows: lung dysfunction: respiratory rate > 20 or $PaCO_2$ < 32 mm Hg; kidney dysfunction: diuresis < 30 ml/h or plasma creatinin > 128 µmol/l; alteration of mental status due to sepsis; liver dysfunction: ASAT > 120 U/l or total plasma bilirubin > 25 mmol/l; lactic acidosis: lactate > 2.44 mmol/l; activation of coagulation.

Sepsis was the reason for admission to the ICU in some patients whereas it occurred as a complication during the ICU stay in others. In these latter cases, day 0 was defined as the first time when the criteria of severe sepsis or septic shock were fully met. If severe sepsis preceded for a few hours a full picture of septic shock, the patient was classified as septic shock. When more than one episode of severe sepsis or septic shock occurred, only the worst was analyzed.

Data collection

The following data were collected at day 0: diagnosis (severe sepsis or septic shock), clinical diagnosis of infection, blood culture results, sex, age, body mass index (kg/m2), body temperature (°C), white blood cell count (G/l), immature white blood cells (%), alveolo-arterial oxygen gradient (mm Hg), Swann-Ganz catheter measurements, number of organ failures, APACHE II (11), duration of follow-up, survival at end of follow-up.

Data about long-term survival and general health of patients released from the ICU were obtained by mean of a questionnaire sent to their physician. The following questions were asked: new underlying diseases and disabilities, further hospitalizations, date of last follow-up and, when applicable, date and cause of death. When there was no answer to the questionnaire, it was sent a second time. When the patient was no longer followed by the physician or when the physician did not respond to the questionnaire, the patient was contacted by phone. For some patients who were hospitalized again, follow-up information was also collected from their medical file. On the whole, we were able to obtain follow-up data from all but two patients.

Statistical analysis

Statistical analysis was performed using SPSS for Windows release 10.1.0.
Overall survival at 28 days and long term survival (from the 28th day until the end of follow-up) were analyzed using Kaplan-Meyer survival analysis.
For Cox regression survival analysis, clinical or laboratory values were first classified into categories when appropriate.

Variable	*Categories*			
Type of septic episode	Septic shock	Severe sepsis		
Sex	female	male		
Age [years]	<35	35-65	>65	
BMI (body mass index) [kg/m2]	<20	20-30	>30	
Body temperature (rectal) [°C]	<36.5	36.5-38.0	>38.0	
White blood cell count [G/l]	<4	4-12	>12	
Immature white blood cells (bands) [%]	<10	>10		
P[A-a]O^2 (alveolo-arterial oxygen gradient) [mm Hg]	<100	100-200	>200	
Blood culture results	negative	Gram +	Gram -	other
Surgery before septic episode	no	yes		

Admission to ICU with sepsis	no	yes		
Nosocomial infection	no	yes		
Systemic vascular resistance [(dyn·s)/cm^5]	<960	960-1400	>1400	
Number of organ failures	1	2	3	>3
APACHE II without Glasgow	<10	10-20	>20	
APS without Glasgow	<10	10-20	>20	
Chronic health evaluation from APACHE II	0-2	3-5		

Chi-square tests were then performed and variables with non significant distributions were discarded. The remaining variables were then matched with the type of septic episode using bivariate Cox regressions, and the non significant variables were also discarded. The remaining variables were submitted to a stepwise multivariate Cox regression analysis during which the variables with a p-value of more than 0.2 were progressively eliminated with the purpose to retain at the end only variables with p-values < 0.05. Survival curves were then drawn for the variables significantly associated with outcome.

Results

Prevalence of sepsis, reason for admission to ICU and acquisition of infections

From 1990 to 1992, 6864 patients were admitted to the ICU (3735 to the surgical unit and 3109 to the medical unit). 339 septic episodes were detected (169 with severe sepsis and 170 with septic shocks). Therefore the prevalence of septic episode, severe sepsis and septic shock in the ICU was: 4.94%, 2.46 and 2.48 % respectively. The number of patients with sepsis in surgical and medical ICUs, the reasons for admission to ICU and the type of acquisition of infection are summarized in table 1.

Microbiological documentation of sepsis

Micro-organisms were isolated from blood cultures in 32% of patients. Blood cultures isolates are listed in table 2. When blood cultures were classified according to the type of isolates (Gram negative bacteria, Gram positive bacteria, other micro-organisms or no micro-organism isolated), no correlation was found with 28-days- or long-term survival.

Sources of follow-up

The data for the patients' follow-up were drawn from the following sources: hospital files in case of new hospitalization, questionnaires sent to physicians or outpatients' clinics, or phone call to the managing physicians or the patients themselves (table 3).

Survival Analysis

1) Kaplan Meyer survival analysis

1.1) 28-days survival

Nineteen out of 170 patients with severe sepsis (11.2%) died during the first 28 days, compared to 93 out of 169 patients with septic shock (55.0 %) ($p<10^{-5}$) (figure 1).

1.2) Long term survival (from the 28th day to the end of follow-up)

Twenty-seven out of 151 patients with severe sepsis who survived the 28th day (16.6%) died during the long term follow-up, compared to 15 out of 76 patients with septic shock (19.7 %) (N.S.). The overall mortality was about 7% at one year and 15% at two years (figure 2).

2) Cox Regression Survival Analysis

Univariate and bivariate analysis allowed removing variables which were not significantly associated with outcome. The remaining variables were then submitted to a stepwise multivariate procedure.

2.1) 28-days survival

The following variables were significantly associated with the 28-days mortality: type of episode (severe sepsis vs. septic shock, p=0.001), age (<35 y, p=0.02; 35-65 y, p=0.13; >65 years, p=0.02), acute physiology score (APS) (<10 points, p=0.02; 10-20 points, p=0.40; >20 points, p=0.02) and the number of organ dysfunctions (1, p=0.10; 2, p=0.62; 3, p=0.20; >3, p=0.04) (figure 3).

Both Kaplan Meyer and Cox regression survival analysis showed a very sharp initial mortality in patients with septic shock. This sharpness is partly an artifact due to the retrospective nature of the study: when the beginning of the septic episode was difficult to determine, day 1 was defined as the acme of the episode. This was followed by a slightly increased mortality until day 28 in patients with septic shock compared to severe sepsis, which was due to the lethal progression of acute organ dysfunctions.

2.2) Long term survival (survival from the 28th day to the end of follow-up)
The following variables were significantly associated with long term mortality: the chronic health points from the APACHE II score (p=0.02), the age (<35 y, p=0.05; 35-65 y, p=0.25; >65 y, p=0.02) and surgery before the septic episode (p=0.02) (figure 4). The type of episode (severe sepsis vs. septic shock, the strongest predictor of 28-days mortality) (figure 4), as well as other markers of sepsis severity (APS, number of organ dysfunctions) (curves not shown) were not significantly associated with long term outcome.

Discussion

Advances in the treatment of severe sepsis and septic shock are needed since mortality remains very high despite the best available care (2, 3). When this study was undertaken, several new approaches were under investigation, such as anti-endotoxin antibodies and various drugs or antibodies aimed at regulating the inflammatory or coagulation cascades (12, 13, 14, 15, 16, 17). However, the long term survival of septic patients was not well known, because most of the available studies examined 28-days survival.

This retrospective study including all patients who suffered from severe sepsis and septic shock in the surgical and medical ICU of the CHUV in Lausanne from 1990 to 1992 was undertaken to improve knowledge on long term survival. We first assessed the 28-days survival in our patients and found that it was similar to published data. Thus, our cohort of patients was a fair representation of the population of septic patients in other studies. We then analyzed the long term survival of the patients who were alive after 28 days. Follow up information was obtained for all but only two patients. Mean follow-up was 25.1 month (5700 patient-months). We found that the overall mortality inferred from the Kaplan-Meyer curve was about 7% at one year and about 15% at two years. The long term mortality was significantly associated with the age, the chronic health points from the APACHE II score and whether surgery had been performed before the septic episodes. The severity of the septic episodes was not a predictor of the long term mortality, in sharp contrast with the 28-days mortality. These findings allow us to conclude that the overall survival of septic patients is mainly related to their underlying conditions, and not to the septic episode itself.

Other studies of long term survival after sepsis have been published more recently. Perl et al. have examined long term survival of 103 patients in the University of Iowa Hospitals and Clinics, meeting the consensus criteria of organ failure and sepsis (1), and who were enrolled into a double-blind placebo controlled efficacy

trial of monoclonal antiendotoxin antibody from 1986 to 1990. Follow up was 877 days. The study was limited to patients with suspected gram negative sepsis and has been published in 1995 (7). The strongest predictor of long term survival in the study model was the severity of underlying diseases as classified by McCabe and Jackson. The authors found that physical dysfunction and more poorly perceived general health occurred commonly after sepsis. 30 day mortality was 32 % and mortality at one year 47 %, which means that 15% of patients surviving after 30 days died during the 11 following months. The long term impact of the type of episode (severe sepsis vs. septic shock) on the 28-days survivors was not analyzed.

Quartin et al. examined survival of 1505 patients with sepsis enrolled in a Study of corticosteroids of whom 45% had septic shock, 15% severe sepsis and 40% uncomplicated sepsis. The study, published in 1997, was conducted from 1983 to 1986 in Veteran Affairs Medical Centers in the United States. Survival was followed during 8 years and compared to a control population consisting of all non psychiatric and non infected patients hospitalized in the participating hospitals during the year 1985 (18). The authors found that the septic population was at significant risk of dying of nonseptic causes and that their overall mortality was higher than controls for the first 5 years. Mortality was 50% at 30 days and 23% of the 30-days survivors died during the 11 following months. This is clearly higher than our findings, reflecting probably the presence of higher age and comorbidities in Veterans' Affair facilities. They mentioned that the overall one year mortality was 71% for severe sepsis and 80% for septic shock, but they did not report the one year mortality in the 28-days survivors.

Weyecker et al. conducted a large scale retrospective cohort study including more than 16'000 patients with ICD-9-CM codes suggestive of infection and organ dysfunction recruited from a U.S. health insurance claims database covering approximately three million members during a period of 10 years from 1991 to 2000. Follow up was 5 years. The study has been published in 2003 (4). The mortality was 21.2% during hospitalization, 51.4% at 1 year, 64.8 % at 3 years and 74.2% at 5 years. The long term mortality was thus higher than our findings, which is probably explained by differences between both populations. Indeed, the criteria for admission into their study were not based on the Bone's definition for sepsis. In addition, 81 % of their patients were older than 65 years, whereas the mean age in our study was 54.7 years.

Angus et al. examined long term survival of 1690 patients with severe sepsis enrolled in the international multiple-center trial of drotrecogin alpha (recombinant activated Protein C) vs. placebo (PROWESS). Patients were enrolled from 1998 to 2000 and followed for a maximum of 3.6 years. The results were published in 2004 (9). The population of patients in this study was probably closely related to our own study population, since similar criteria were used for sepsis definition (19), patients were treated in intensive care units and ages were similar (mean ages were 50.4 years in placebo and 54.2 years in drotrecogin alpha vs. 54.7 years in our population). However, the patients' septic episodes were not classified into severe sepsis or septic shock. While early survival benefit was observed in subjects with APACHE II scores ≥25 receiving drotrecogin alpha, this advantage lost statistical significance after hospital discharge. Overall survival rates for drotrecogin alpha vs. placebo were 66.1% vs. 62.4% at 3 months, 62.2% vs. 60.3% at 6 months, 58.9% vs. 57.2% at 1 year, and 52.6% vs. 49.3% at 2 ½ years. Thus long term mortality was comparable to our findings.

Twenty years after collecting our data, the overall mortality of severe sepsis and septic shock remains unfortunately virtually unchanged. Innovative approaches are still elusive. Our data, as well as others, suggested that patients after septic episodes had acceptable long term survival dictated mainly by their underlying conditions. In particular, our study is the only one which clearly demonstrated that the severity of the septic episode (severe sepsis vs. septic shock) was not related to long term survival in 28-days survivors. These findings justify the allocation of substantial resources to research on the treatment of these conditions, given their high incidence in intensive care units, their high immediate mortality, and the good prognosis of survivors.

References

1. Bone RC, Balk RA, Cerra FB, Dellinger RP; Fein AM, Knaus WA, Schein RM, Sibbald WJ. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 1992; 101 : 1644-1655.
2. Angus DC, Wax RS. Epidemiology of sepsis: an update. Crit Care Med 2001; 29 (July Suppl) : 109-116.
3. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med 2003; 348 : 1546-1554.

4. Weycker D, Akhras KS, Edelsberg J, Angus DC, Oster G. Long-term mortality and medical care charges in patients with severe sepsis. Crit Care Med 2003; 31 : 2316-2323.
5. Angus DC, Linde-Zwirble WT; Lidicker J, Clermont G; Carcillo J, Pinsky R. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med 2001; 29 : 1303-1310.
6. Friedman G, Silva E, Vincent JL. Has the mortality of septic shock changed with time? Crit Care Med 1998; 26 : 2078-2086.
7. Perl TM; Dvorak L; Hwang T, Wenzel RP. Long-term survival and function after suspected gram-negative sepsis. JAMA 1995; 274 : 338-345.
8. Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis. N Engl J Med 2003; 348: 138-150.
9. Angus DC, Laterre PF, Helterbrand J, Ely EW, Ball DE, Garg R, Weissfeld LA, Bernard GR; PROWESS Investigators. The effect of drotrecogin alfa (activated) on long-term survival after severe sepsis. Crit Care Med 2004; 32 : 2199-2206.
10. Vereinigung Schweizerischer Krankenhäuser (VESKA), eds. Diagnosenschlüssel 1979 nach der internationalen Klassifikation der Krankheiten (ICD) der WHO, 9. Revision. Aarau, VESKA Verlag, 5e éd, 1991.
11. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985; 13 : 818-829.
12. Baumgartner JD. Monoclonal anti-endotoxin antibodies for the treatment of gram-negative bacteremia and septic shock. Eur J Clin Microbiol Infect Dis 1990; 9 : 711-716.
13. Calandra T, Glauser MP. Cytokines and septic shock. Diagn Microbiol Infect Dis 1990; 13 : 377-381.
14. Cohen J, Glauser MP. Septic shock: treatment. Lancet 1991; 338 : 736-739.
15. Glauser MP, Heumann D, Baumgartner JD, Cohen J. Pathogenesis and potential strategies for prevention and treatment of septic shock: an update. Clin Infect Dis 1994; 18 Suppl 2 : 205-216.
16. Calandra T, Baumgartner JD, Glauser MP. Anti-lipopolysaccharide and anti-tumor necrosis factor/cachectin antibodies for the treatment of gram-negative bacteremia and septic shock. Prog Clin Biol Res 1991; 367 : 141-159.
17. Baumgartner JD, Eggimann P, Glauser MP. Management of septic shock: new approaches. Curr Clin Top Infect Dis 1992; 12 : 165-187.
18. Quartin AA, Schein RM, Kett DH, Peduzzi PN. Magnitude and duration of the effect of sepsis on survival. Department of Veterans Affairs Systemic Sepsis Cooperative Studies Group. JAMA 1997; 277 : 1058-1063.

19. Gordon RB, Vincent JL, Laterre PF et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. The Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) Study Group. N Engl J Med 2001; 334: 699-709.

Acknowledgements

Je remercie le Professeur Jean-Daniel Baumgartner pour son soutien tout au long de cette étude et le Dr. Philippe Sudre pour son aide pour l'analyse statistique.

Table 1. Number of patients in surgical and medical ICUs, reasons for admission to ICU and type of acquisition of infection.

	All	*Severe Sepsis*	*Septic Shock*
Type of ICU			
Surgical unit	185	88	97
Medical unit	154	81	73
Total	*339*	*169*	*170*
Reason for admission to ICU			
Sepsis	223	97	126
Acute disease other than sepsis	70	42	28
Postoperative management	25	18	7
Trauma	12	10	2
Late postoperative complication	7	2	5
Other	2	2	
Acquisition of infection			
Community-acquired	179	72	107
Hospital-acquired	160	98	62

***Table 2**. Results of blood cultures.*

	All episodes	***Severe sepsis***	***Septic shock***
All patients	339	169	170
Patients with positive blood cultures (%)	109 *(32)*	43 *(25)*	66 *(39)*
Number of micro-organisms isolated	138	49	89
Gram positive			
Streptococcus pneumoniae	21	7	14
Staphylococcus aureus	17	9	8
Other aerobic streptococcus	16	8	8
Staphylococcus epidermidis	13	7	6
Streptococcus pyogenes	4	1	3
Other gram positive	3		3
Total Gram positive (%)	74 *(53.6)*	32 *(65.3)*	42 *(47.2)*
Gram negative			
Escherichia coli	26	6	20
Enterobacter sp	6	1	5
Klebsiella sp	5	2	3
Pseudomonas aeruginosa	3	1	2
Other gram negative	11	2	9
Total Gram negative (%)	51 *(36.9)*	12 *(24.5)*	39 *(43.8)*
Anaerobes (n, %)			
Bacteroides fragilis	3		3
Other anaerobes	2	1	1
Total anaerobes (%)	5 *(3.6)*	1 *(2.0)*	4 *(4.5)*
Fungi			
Candida sp	7	4	3
Other fungi	1		1
Total fungi (%)	8 *(5.8)*	4 *(8.2)*	4 *(4.5)*

Table 3. Source of data for the 227 patients surviving more than 28 days.

Source of follow-up	*Family doctor*	*Out-patients' clinic*	*Patient himself*	*Total*
Death during hospital stay				11
New hospitalization				11
Questionnaire	125	16		141
Phone call	21	8	33	62
Lost for follow-up				2
Total				227

Figure 1. Kaplan-Meyer 28-days survival analysis of patients with severe sepsis or septic shock.

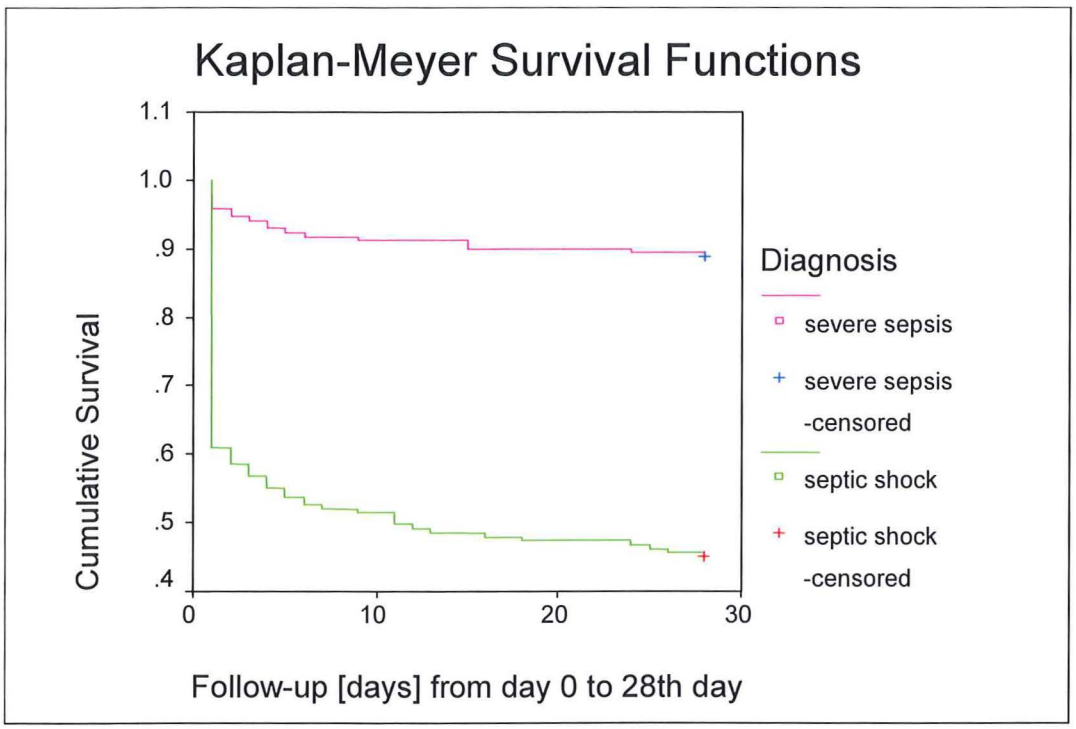


Figure 2. Kaplan-Meyer long term survival analysis of patients with severe sepsis or septic shock who survived the first 28 days

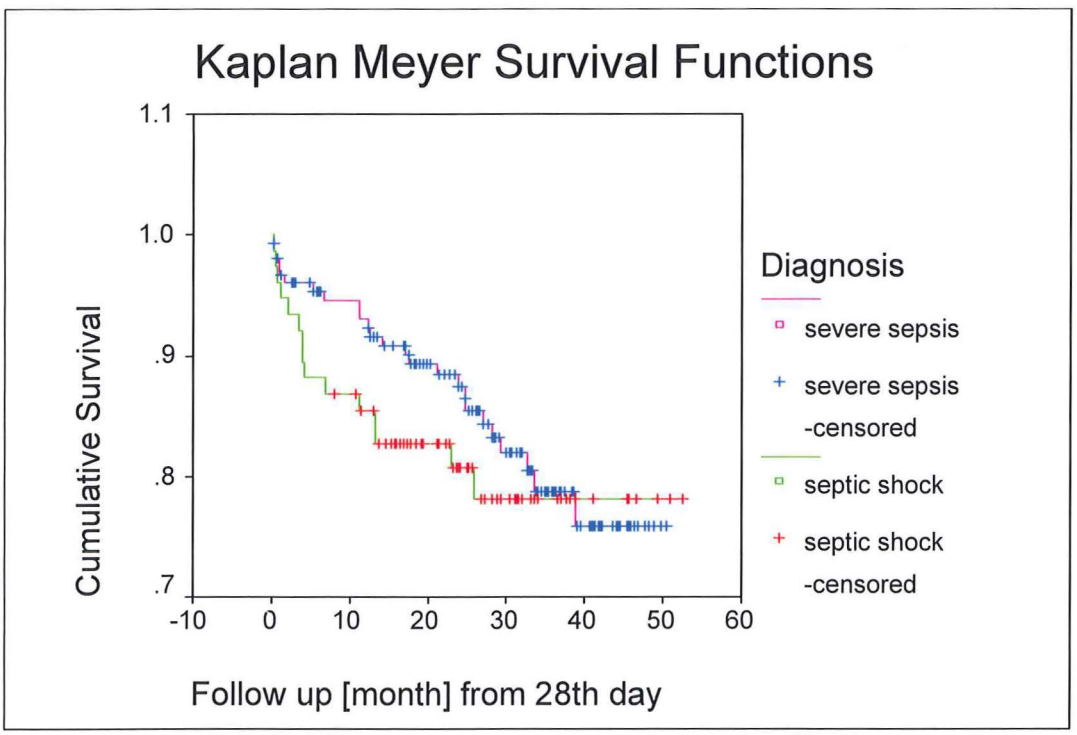


Figure 3. 28-days Cox regression survival analysis.
Figure 3.1. Comparison of patients with severe sepsis or septic shock

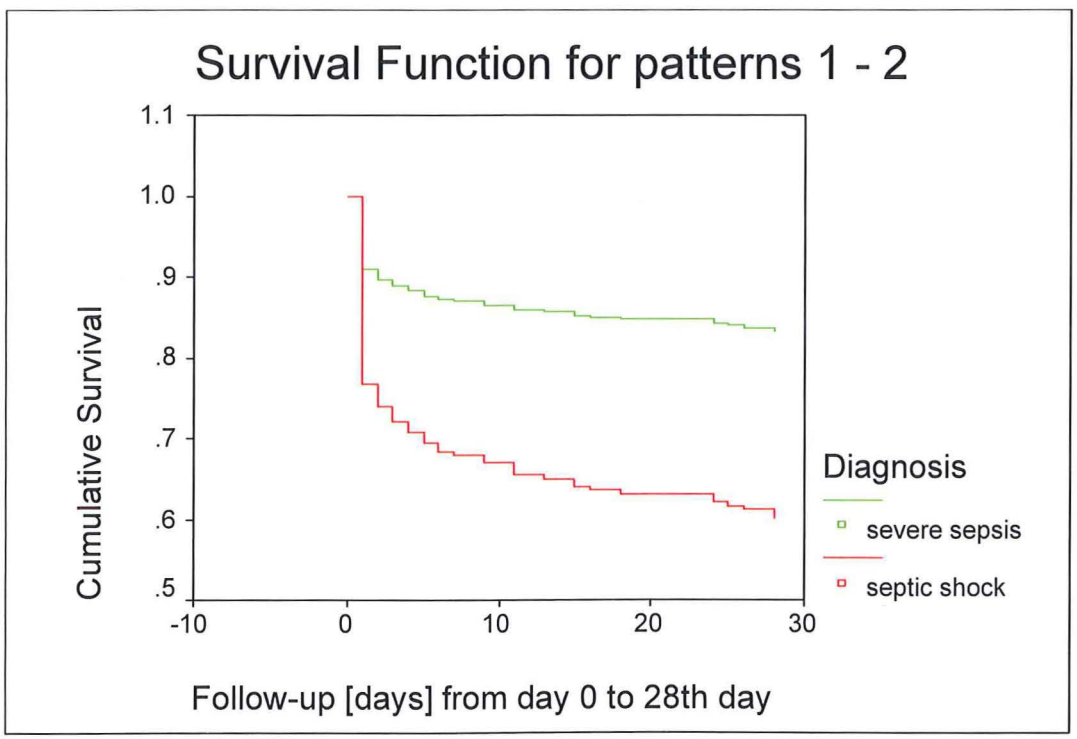


Figure 3.2. Comparison of patients <35, 35-65 or >65 years old

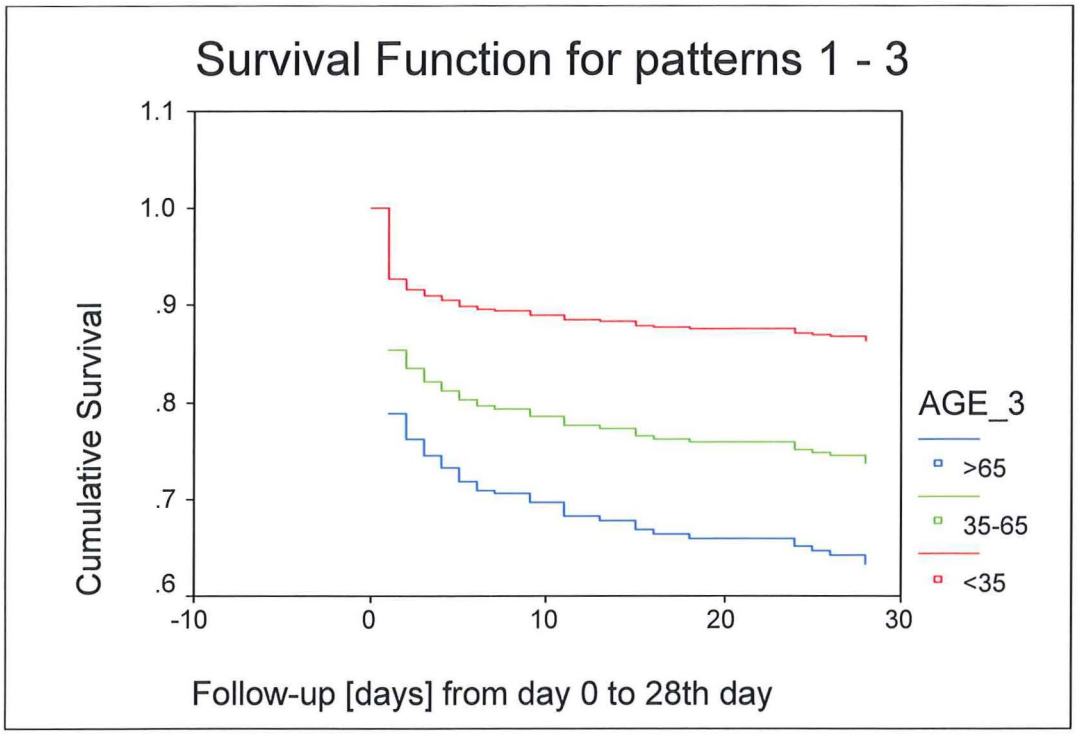


Figure 3.3. Comparison of patients with acute physiology score <10, 10-20 or >20 points

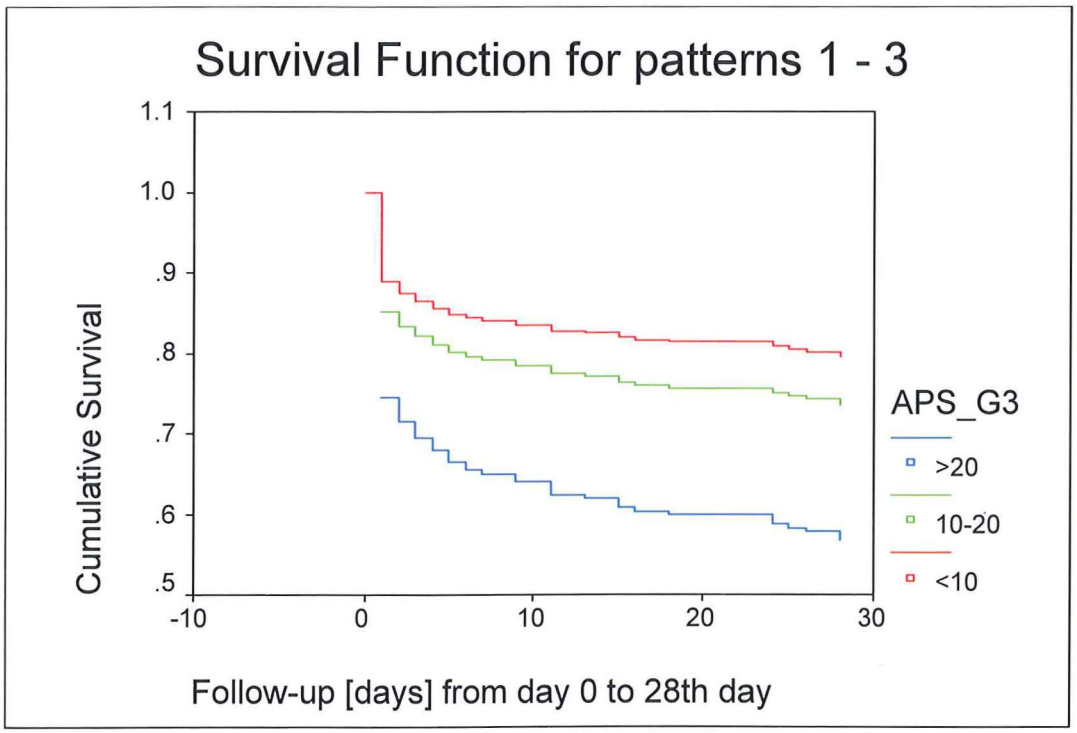


Figure 3.4. Comparison of patients with 1, 2, 3 or >3 organ failures

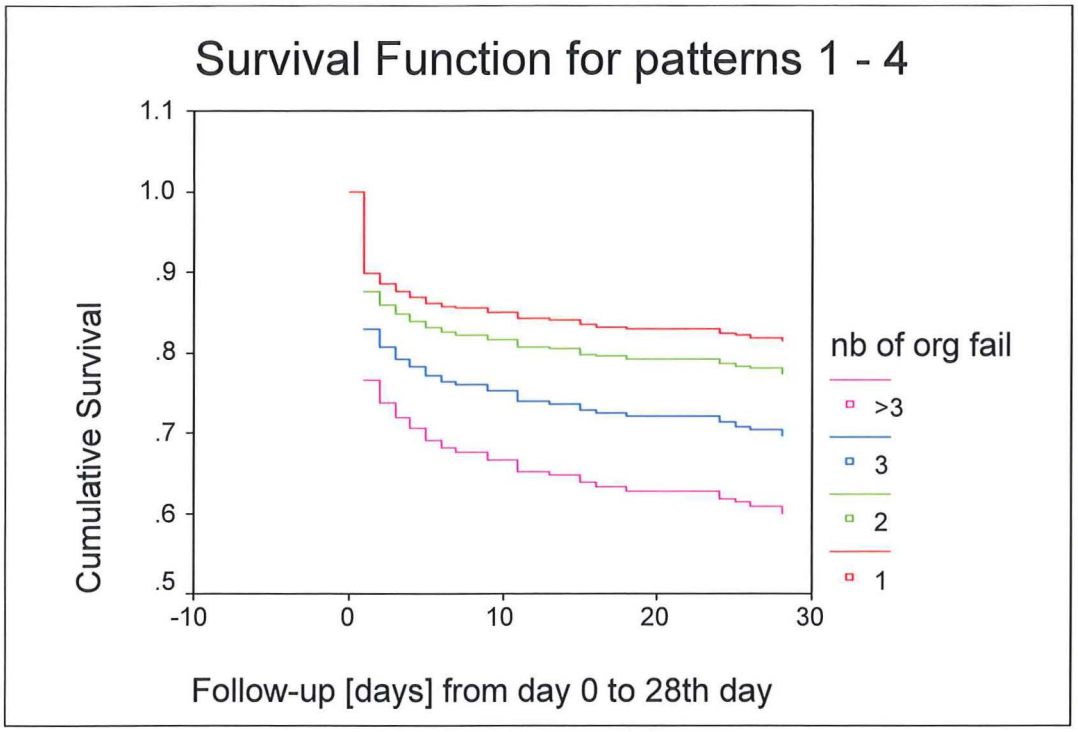


Figure 4. Long term Cox regression survival analysis of the patients who survived more than 28 days.

Figure 4.1. Comparison of patients with severe sepsis or septic shock

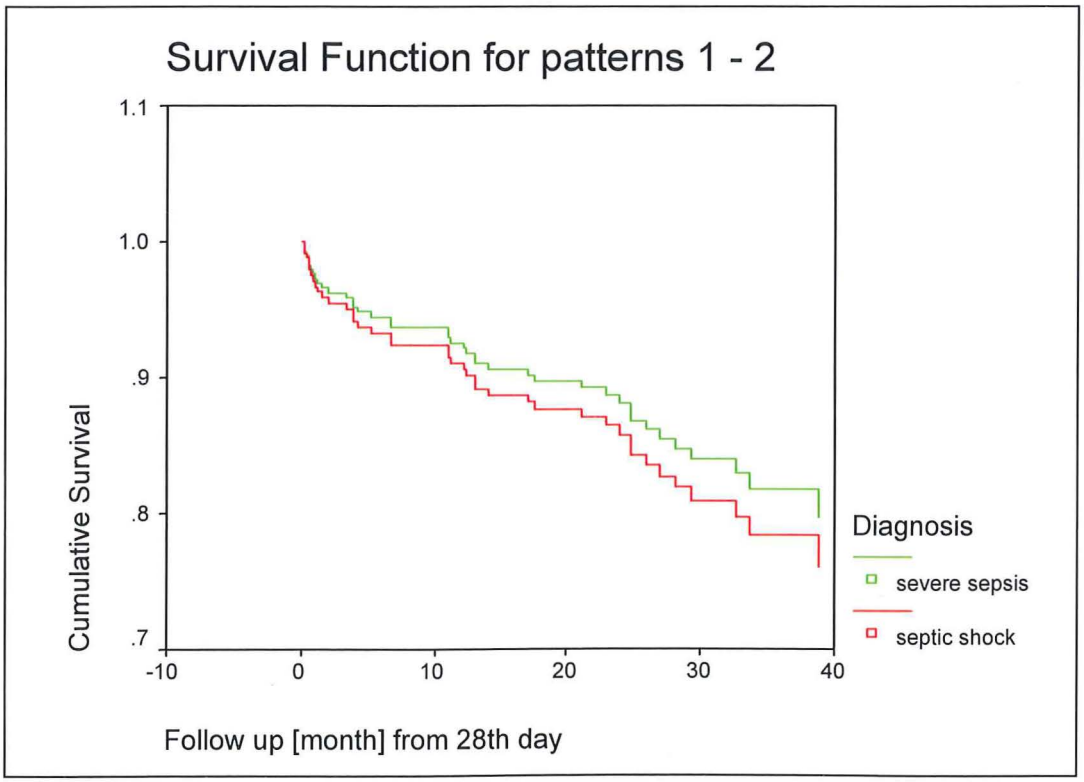
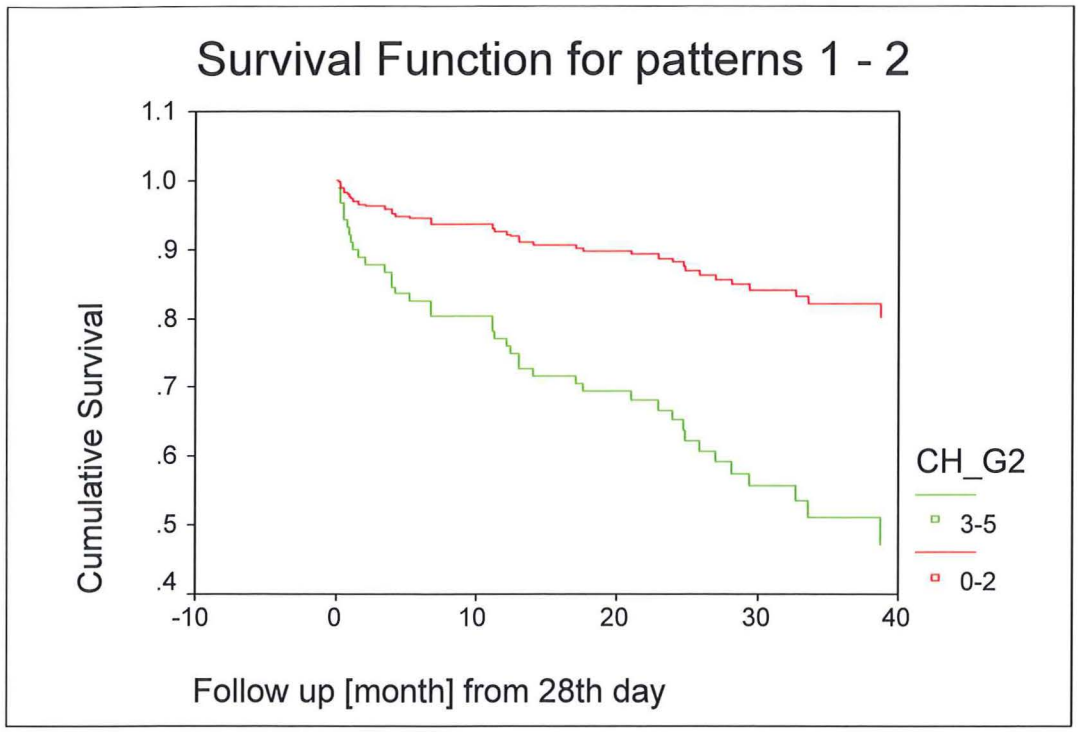


Figure 4.2. Comparison of patients with 0-2 or 3-5 chronic health points from the APACHE II score



CH_G2 = chronic health points from APACHE II

Figure 4.3. Comparison of patients <35, 35-65 or >65 years old

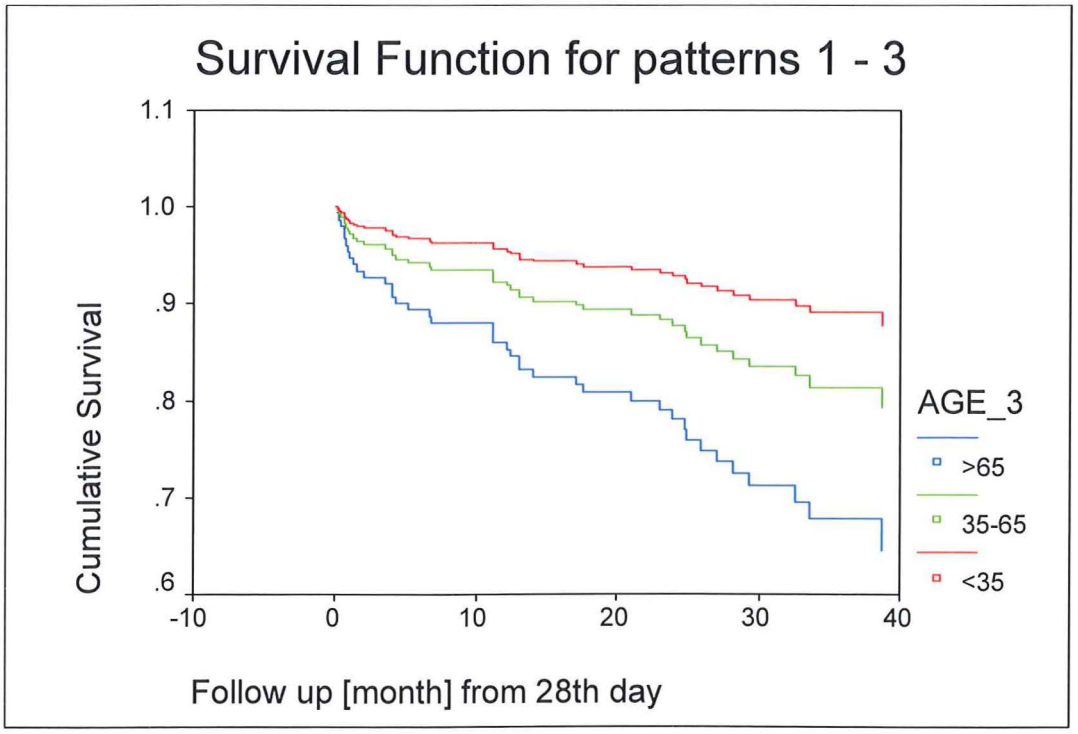
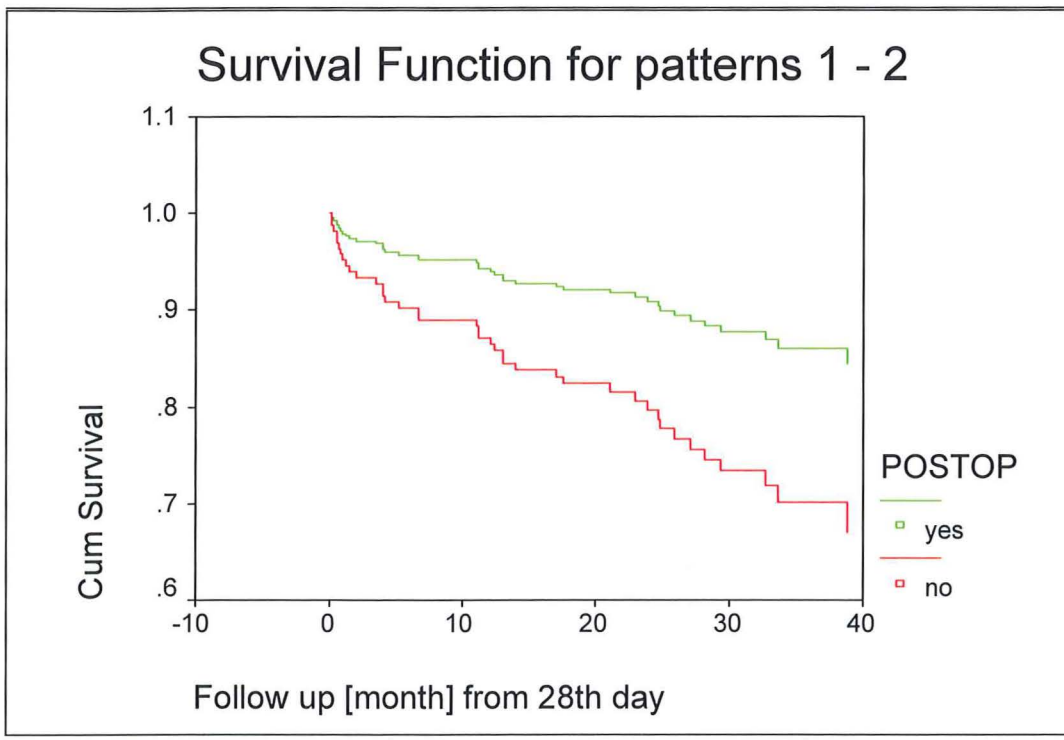


Figure 4.4. Comparison of patients with or without surgery



POSTOP = postoperative status