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Sequential Organ Failure in Cancer Patients Admitted To the Intensive Care Unit at the National Oncologic Institute in Ecuador

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RESUMEN

Introducción.- Pacientes con cáncer están expuestos a varias complicaciones amenazantes de su vida, ya sea por el agresivo régimen de quimioterapia o por la enfermedad subyacente. A estos pacientes cuya estancia en UCI podría ser cuestionada una evaluación del pronóstico podría sería de ayuda.

Objetivos.- Es evaluar la severidad de la secuencial falla de órganos "Sequential Organ Failure Assessment (SOFA) score" en pacientes oncológicos ingresados en el Servicio de Medicina Intensiva del Instituto Oncológico Nacional SOLCA. Guayaquil-Ecuador.

Diseño- Prospectivo descriptivo con seguimiento extrahospitalario

Materiales y Métodos.- Se realizó un estudio prospectivo en la que se analizó a 50 pacientes, desde su período de ingreso en UCI hasta su fallecimiento o alta hospitalaria con el respectivo seguimiento extrahospitalario. Los pacientes ingresados UCI con diagnóstico citopatológico confirmado de cáncer y que reunieron las siguientes características fueron incluidos: Permanencia en UCI > 48 horas, pacientes con cáncer no localmente avanzado complicados, pacientes con cáncer localmente avanzado complicado post-quimioterapia o radioterapia, los con cáncer regionalmente avanzado vírgenes de tratamiento oncológico. Fueron excluidos. Pacientes con menos de 48 horas de ingreso en UCI, los con cirugía electiva no complicada, los con cáncer regionalmente avanzado que a pesar de un régimen de tratamiento previo, su enfermedad haya continuado en progresión. Los pacientes estudiados fueron valorados y agrupados en: Tumores sólidos y enfermedades hematológicas malignas. El poder predictivo del Sequential Organ Failure Assessment (SOFA) score" fue valorado con la curve receiving operative (ROC) y el análisis de regresión de Cox fue usado para identificar los posibles efectos de las covariables en la sobrevida de los pacientes

Resultados.- Del total de 50 pacientes estudiados fueron hombres 22 (44%) y mujeres 28 (56%), con una media de edad de 54.94 ± 17.81 DE un valor promedio de APACHE II de 23.56 ± 6.76 DE y un score SOFA promedio de 8.22 ± 3.97 DE. Las causas más frecuentes de ingreso a UCI correspondieron a: IRA hipoxemica 21 (42%), IRA por hipoventilación 9 (18.%), shock septico 9 (18.%) y descompensación metabólica 7 (14%). Al evaluar la severidad de la secuencial falla de órganos "Sequential Organ Failure Assessment (SOFA) score" a través de la curve reiceving operative (ROC), encontramos un área bajo la curva de 0.90 (CI 0.81-0.98) SE 0,045. El modelo de regresión de Cox demostró un coeficiente beta de 2,06 (SE 0.88) $p < 0.001$ para falla respiratoria , de 1,25 (SE 0.8). $p < 0.001$ para número de fallas orgánicas. El porcentaje de sobrevida acumulada es de un 20% a los 3 años.

Conclusiones.- Para pacientes con cancer hospitalizados en UCI la severidad de la enfermedad y el riesgo de muerte puede ser valorado agudamente por el SOFA 0.90 (CI 0.81-0.98) SE 0,045 . Con menor probabilidad de supervivencia para los pacientes con falla respiratoria y el número de fallas orgánicas.

ABSTRACT

Background. Cancer patients experience life threatening complications related to their chemotherapeutic regimen or underlying neoplastic disease. A prognostic assessment is helpful to evaluate patients admitted to the Intensive Care Unit (ICU). We intend to assess the severity of organ dysfunctions in cancer patients utilizing the Sequential Organ Failure Assessment (SOFA) score.

Methods. We followed 50 cancer patients from their admission to the ICU until their discharge from the unit or their demise in a prospective descriptive observational study. Selected patients were grouped for their evaluation in two categories: solid tumors or hemato-oncologic diseases. The predictive power of the SOFA score was validated. Results._ The average of the Acute Physiology And Chronic Health Evaluation II (APACHE II) and SOFA scores obtained was 23.56 (± 6.76 SD) and 8.22 (± 3.97 SD) respectively. The following number of patients was admitted to the ICU with the concomitant conditions: Acute Respiratory Insufficiency (ARI) with hypoxemia 21 (41%), ARI with hypoventilation 9 (18%), septic shock 9 (18%), and metabolic decompensation 7 (14%). The Cox regression model showed a beta coefficient of 2.06 ($p < 0.001$; SE 0.88) for patients with respiratory failure, and a value of 1.25 ($p < 0.001$; SE 0.8) for systemic organ failures. The 3-year survival rate observed was 20%. Conclusions._ Illness severity and death risk for cancer patients admitted to the ICU can be evaluated with the SOFA score. After 30 months at follow up, we found a decreased survival rate for patients with respiratory failure and patients with an elevated number of organ failures.

TABLE OF CONTENTS

INTRODUCTION

Patients with cancer may develop life threatening complications. These complications can be due to their chemotherapeutic regimen, independently from their neoplastic disease clinical course, or due to an acute insult (1).

Even though, some patients have not undergone any chemotherapeutic regimen in the past, an acute insult by itself can complicate their disease clinical course (2,3), and due to the need for a rigorous monitoring and support during these episodes, it is imperative that they be transfer to the ICU immediately (4).

Among all the patients admitted to the ICU, neoplastic patients have always presented with dismal outcomes and mortality rates up to 70 to 80% in some series (5-8). Due to this unfortunate prognosis, some clinicians and centers refuse to admit these type patients to the ICU (9). However, recent studies have shown that this approach is not justified by any clinical background, since criteria for patients' admittance to the ICU is based in certain prognostic factors (10). Nevertheless, prognosis for patients with solid tumors and hemato-oncologic diseases remains controversial, and admittance of these patients bears difficulties regarding their clinical and ethical management, and also the cost-benefits of their care (11,12).

Ferraris, et al. showed that multiple organ dysfunctions represent an important risk factor when establishing mortality probabilities among patients in the ICU (13).

There are few studies attempting to ascertain the role of multiple organ dysfunctions in patients with cancer. Hence, it is essential to perform risk stratification on patients with cancer, knowing by these means, which patients will benefit form the additional support provided in to the ICU.

The purpose of this study is to assess the magnitude of the relation involving organ failure and patients' demise, and the impact that each one of the co-variables has in the out and in-hospital survival rates among neoplastic patients previously admitted to the ICU at the National Oncologic Institute "Dr. Juan Tanca Marengo" in Guayaquil-Ecuador.

MATERIALS AND METHODS

We designed a prospective descriptive observational study with follow-up after discharge. Patients admitted to the ICU at the National Oncologic Institute "Dr. Juan Tanca Marengo" from January 1998 to January 2000 were included in the study.

The following inclusion criteria were considered: patients admitted to the ICU diagnosed with cancer confirmed by cytopathologic sampling and analysis; permanence at the ICU for more than 48 hours; non-locally advanced neoplastic disease with complications; locally advanced neoplastic disease (without evidence of regional extension) previously treated with chemotherapy or radiotherapy with complications; regionally advanced neoplastic disease which has not received chemotherapy or radiotherapy in the past; patients not previously admitted to the ICU.

Patients with the following criteria were excluded: patients with permanence at the ICU of less than 48 hours, patients who underwent an elective surgical procedure and didn't present any complications; patients with regionally advanced neoplastic disease which had progressed despite of being under a therapeutic regimen.

Patients included in the study were evaluated and grouped according to their neoplastic disease stage: solid tumors (stages I-IV), or hemato-oncologic diseases such as lymphoma (stages I-IV) and myeloma (stages I-III). Patients with leukemia were not included in the study because we attempted to establish a correlation between the initial neoplastic disease stage and the patients' prognosis and due to a different classification system for leukemia; it is not feasible to ascertain this correlation.

Data were recollected in a standard registry which included information as: age, sex, diagnosis at admission, histopathologic diagnosis, APACHE II score (13), Simplified Acute Physiology Score II (SPAS II) (13), and most common sites or sources for infection (respiratory tract, urinary tract, catheters, blood, peritoneum, wounds, etc).Multiple organic dysfunctions were evaluated with the SOFA score, proposed by Vincent, et al. (14,15) on a daily basis.

Statistical analysis

Results were expressed as: mean ± standard deviation. Categorical variables were analyzed with the X^2 test and continuous variables with the student's test. Statistical significance was considered if $p < 0.05$.

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and ROC (16) were calculated to assess de efficacy of the SOFA score (15). After hospital discharge, each patient was followed-up to 30 months. This was accomplished mainly with regular visits to the clinic by the patients and periodic check ups. Patients who discontinued attending to the expected check ups, were contacted by phone

or visited at home by a physician to establish their final outcome. The Kaplan Meier method was utilized to measure patient's survival rate after discharge, and the Long-rank test was employed to establish differences between curves obtained during the analysis (17)

Prognostic factors representing statistical significance with the univariable model were included in the Cox model with the purpose of determining the impact that each one of the covariables has in patients' survival rate (18,19). The American College of Chest Physicians & Society of Critical Care Conference criterion for sepsis and organic failure were employed in this study (20).

RESULTS

A total of 50 patients were included in the study. Out of those patients, 22 (44%) were male. The mean age was 54.94 ±17.81 SD (Table 1).

The most common conditions for admission to the ICU were: ARI with hipoxemia 22 (42%), ARI with hypoventilation 9 (18%), septic shock 9 (18%), metabolic decompensation 7 (14%)., cardiogenic shock and gastrointestinal bleeding 3 (6%).

Regarding the nature of cancer, patients presented within the following categories at admission: cervical cancer 7 (14%), non-Hodgking lymphoma 10 (20%), brain tumors 7 (14%), colon cancer 4 (8%), breast cancer 3 (6%), thyroid cancer 2 (4%), lung cancer and two others solid tumors 5 (10%) and solid tumors with metastasis 10 (34%)

Tumor stages exhibited the following prevalence percentages: stage III 27 (54%), IV 10 (20%), II 10 (20%) and I 3 (6%) (17). Within cancer patients', 60% of patients who didn't

survive due to their deteriorating disease course, presented an increase of 80% at their SOFA score that was measure during the study , compared with only 20% of patients who survived. Mortality rate for patients with failure ≥ 4 organs was 80%, whereas for patients with failure ≤ 3 organs was 20%.

Scores of ≤ 11, were associated with a mortality rate of 34.3%, while scores of ≥11 correlated with a mortality rate of 80% (sensitivity 50%, specificity 90%, PPV 80%, NPV SOFA 65.7%, accuracy 70%) ROC 0.90 (CI: 0.81-0.90) SE 0.45 (Figure 1)

The overall mortality rate for patients in the ICU was 48%. APACHE II, SOFA, and (SAPS II), (table 2). Scores were higher for patients who didn't survive due to their adverse clinical course in comparison with patients who continued alive until the end of the follow-up period (table 2).

Mortality rates according with tumor stages were as follows: stage I (8.3%), II (16.7%), III (45.8%) and stage IV (29.2%).

Infectious pathogens were isolate in 26% of patients. Patients with positive pathogen isolation had a more severe degree of organic dysfunction with a higher SOFA score. Mortality rate for patients with a positive pathogen isolation was 53.8% (7 patients), whereas for those with a negative pathogen isolation was 45.9% (17 patients) with no statistically significant difference. Mortality rate increased as the number of organs involved increased. For 2 organs failure, the mortality rate was 9%, for 3 organs failure was 20%, for 4 organs failure was 77% and for 5 organs failure was 83%, this differences was statistically significant.

Although there were not statistically significant differences as the number of organ failures increased, the probability for detecting and isolating an infectious pathogen increased as well. Thus, in patients with ≥ 4 organs failure, the probability of isolating a pathogen was 61.6%, whereas in patients with ≤ 3 organs failure was 54 % (p = 0.3). The most frequent isolated pathogens were: *Pseudomonas aeriginosas* 4 (20%), *Klebsiella Pneumoniae* 3 (15%), *Staphylococcus coagulasa* 3 (15%), *Acinectobacter* 2 (10%), *Candida albicans* 2 (10%), *Enterobacter cloacae* 2 (10%), *Pseudomonas cepacea* 2 (10%), *Enterobacter aerogenes* 1 (5%) and *Escherichia coli* 1 (5%). The most common sources for pathogen isolation were: blood cultures 33.3%, respiratory tract 46.6%, catheters 6.7% and urine 13.3%. Survival rate was 28% after 30 months of follow-up.

Mortality at discharge was 48%, it was higher in higher tumor stages. After the 30 months of follow-up, cancers with stage II presented a mortality rate of 22.2%, for stage III mortality was 55.5% and for stage IV was 85.7%. Two patients with stage IV disease, one diagnosed with choriocarcinoma and lung metastasis, and the other with ovarian cancer and lung metastasis, were still alive. Neither of them underwent anti-neoplastic treatment (chemotherapy, radiotherapy, hormonal therapy or surgery).

The survival rates of patients in ICU shows a statistical significance between the two main groups of cancer with solid tumors and hemato-oncologic diseases (lymphomas and myelomas) showing a Cox-Mantel Log-rank (p = 0.01). Statistical significance was demonstrated in the corresponding survival rates for the two groups of cancer patients after discharge from ICU (Cox-Mantel Log-rank p = 0.04).

(Figure 2).

Using the univariable model, mortality related to multiorgan failure revealed significant differences for the following groups: respiratory failure 42% ($p = 0.001$), renal failure 2%($p = 0.001$), cardiovascular failure 6% ($p = 0.003$). The Cox model for proportional risk, showed beta coefficients of 2.05 (SE:0.88) for respiratory failure, and 1.12 (SE: 0.8) for the number of organs affected (table 3)

DISCUSSION

Although the benefits of admitting patients with cancer to the ICU remains controversial due to their high mortality rates, this study intended to determine the impact that organ failures have in neoplastic patients, and to ascertain prognostic factors that can help us to establish survival rates.

We found that for patients with 4 or more failing organs mortality was 78.7%, whereas for patients with 3 or less failing organs mortality was 9.1%. These results are similar to findings from several other authors who noticed that the number of failing organs had an adverse effect in survival rates, with a correlation between patients who were mechanical ventilated ($r=0.98$) and the increase in the number of systems implicated (21,22). None of the patients who presented with more than 4 dysfunctional organs survived more than 6 months.

We also observed that patients with respiratory and cardiovascular failure had an unfavorable outcome (univariate analysis $p < 0.05$).

Blot, et al. retrospectively followed 107 neutropenic patients admitted to the ICU and found an increase in mortality correlated with respiratory and cardiovascular failure ($p < 0.001$) and

using the logistic regression model for analysis, only multiple organ failure and respiratory failure predicted mortality in the ICU (24). In our study, the absence of statistical significance for neurologic failure and hepatic failure as prognostic factors can be due to a selection bias (type II error) because of a lack of statistical power. This happened for the reason that we have a small sample.

In our analysis, cardiovascular failure was also associated with an adverse prognosis when we used the univariate analysis; but using the multivariate analysis, cardiovascular failure disappeared as a prognostic factor because we use other variables that could influence in the prognosis factor.

Groeger et al., found that patients with progression of their cancer and with severe respiratory failure had approximately twice the probability of dying than patients who didn't presented these characteristics (25). He also found that a severe organic dysfunction is accompanied by the presence of disseminated intravascular coagulation, cardiac arrhythmias and the need for vasopressor support. Patients with cardiovascular failure had two times the probability of dying, while patients with hematologic failure presented with a probability of up to four times.

Using the multivariate analysis, we found that the prognosis in this specific group of patients is clearly not associated to the type of cancer or its progression, and it only depends on the presence and the nature of organ failure. This finding can be due to the fact that we didn't include in our analysis those patients who presented with progression on their cancers' clinical course. This results differ from findings reported in Blot and Groeger studies (24,25).

Among all systemic dysfunctions, respiratory failure related to a prolonged need for mechanical ventilation had a considerable effect on the results we obtained. This do not vary from the results previously published (22,25,26,27,28).

In our investigation, respiratory failure and cardiovascular failure are directly associated with mortality of patients admitted to the ICU. These covariables might influence the out-of-hospital survival rate, as it was expressed by the Relative Risk when we used the Cox model. Nonetheless, we didn't find a relation between the out-of-hospital survival rate and hematologic failure, most likely because we didn't include patients with leukemia in the group of patients with hemato-oncologic diseases. We excluded patients with leukemia due to difference that exist between the classification system for this type of cancer and other neoplastic diseases. Another reason to exclude theses type of patients was because we intended to establish the influence that the progression of the cancer has in patients' prognosis and the initial stage for every neoplastic condition at the time of admission to the ICU as well.

A positive correlation was noted between the SOFA score, obtained during the patients' stay at the ICU, and the mortality rate. Guiguet, et al. found an adequate discriminatory effect when evaluating Organic System Failures (OSF) in neutropenic patients with a ROC of 79±5.0 SD (23). The mortality rate in our group of patients admitted to the ICU corresponded to 48% (24 patients). This percentage is similar to the results reported by Groeger and Soares (58.7% and 42% respectively) on their series (37,38).

The mortality rate in our report, associated to respiratory failure, was 74%. Groeger, et al. established, in a multicentric prospective study carried out in 5 hospitals with 782 patients, a mortality percentage of 76% related to respiratory failure.

We found that the extention of malignity in one specific group of patines with out treatment, do not have any prognosis value. Hence, out of the 52% of patients who survived at discharged from the ICU, 30% had a regionally advanced neoplastic disease whit not chemotherapy or radiotherapy previously (stage III for myeloma and stage IV for solid tumors and lymphomas). The out-of-hospital survival rate for these patients was 5 months.

Two patients were still alive at the time the statistical analysis was done, a patient who presented choriocarcinoma and lung metastasis, and a patient with ovarian cancer and lung metastasis. These patients have a high survival rate but the sample is very small and does not permit for a statistical analysis

Only 2 patients, out of 4 (50%) who were discharged alive and who presented with 4 or more organ dysfunctions, were alive after 2 years and 6 months of follow-up. From 17 patients who presented 3 organ dysfunctions, 13 (76%) were alive after the same follow-up period.

In this study, each and every one of the patients admitted to the ICU with cancer and metabolic disturbances with out organ failure, survived at discharge thanks a good management and the base disease (46 patients). We also noticed a high mortality in patients who presented with ARDS as distinguished from patients with acute lung injury, and we also noticed a better prognosis in patients with metabolic disturbances alone.

Patients' age was not correlated with mortality after performing a univariate analysis ($p = 0.23$). However with multivariable analysis was significant correlate to death age ($p= 0.04$) . This data obtained in our study is different for results obtained in other series (29,30). This finding with univariate analysis is probably due to the fact that elderly patients included in our study presented with cancers related to a less unfavorable prognosis like breast cancer, while

younger patients presented neoplastic diseases with poor prognosis. Nevertheless, the most influential prognostic factors observed for mortality were respiratory failure and an increase in organ dysfunctions, especially at respiratory system.

Limitations:

1. - We consider untreated cancer patients without any evidence of active malignity.

2. - Our work is monocentric that is why we also need validate this work in other ICU's

3. - We also have patients with different kind of solid tumours and the amount of patients may be to small.

We are aware that mortality by itself is considered insufficient criteria to assess ICUs efficiency (36). Consequently, to quantify organ dysfunctions is perhaps a comprehensive method to evaluate the disease severity in patients with cancer. Although patients with 4 or more organ dysfunctions have a bad prognosis, evaluating the outcome that restricting them from the support provided at the ICU or implementing an alternative therapy for them was beyond the scope of this study. The effort and resources employed in this project are aimed to improve the cost-effectiveness on identifying patients with high morbidity and mortality who will benefit from ICU care.

The results that we obtained, shows that the most common multiorgan failure is the respiratory failure. For this reason, is recommendable that the management of this failure should be efficient and well detail for better long term results.

Table 1. Cancer Patients Demographics

VARIABLES	Minimum	Maximum	Mean	Standard Deviation
Age	16	85	54.94	17.81
Days with Organ Dysfunction	1	10	4.18	2.53
Days at the ICU	2	20	5.68	4.21
SOFA score*	2	18	8.22	3.97
APACHE II score**	9	39	23.56	6.76
SAPS II score***	15	73	42.52	12.99
APACHE III**	21	106	64.90	20.95
Pa02/FI02	56	593	227.46	118.50
Bilirrubin	0	19	2.20	3.88
Creatinine	1	14	1.67	2.00
Glasgow Coma Scale	3	15	12.08	3.54
Cancer Stage	1	4	3.06	0.89
Respiratory Score	0	4	2.46	1.28
Cardiovascular Score	0	4	2.12	1.69
Hematologic Score	0	4	1.22	1.36
Hepatic Score	0	4	0.64	1.21
Renal Score	0	4	0.56	1.03
Neurologic Score	0	4	1.22	1.31

† Data are present as numbers. Maximum and minimum values are shown. Mean and standard deviation are also included

* SOFA. Sequential Organ Failure Assessment (SOFA) score

**APACHE. Acute Physiology and Chronic Health Evaluation

*** SAPS II. Simplified Acute Physiology Score II

Table 2. Patients Outcome correlation with APACHE II, SOFA and SAPS II scores†

VARIABLES	**APACHE* II**	**SOFA** Score**	**SAPS*** II Score**	**Days with Organ Failure**
Survivors	20.57±5.65 SD	5.57±3.07 SD	39.65±13.21 SD	3.76±2.25 SD
Non-Survivors	26.79±6.40 SD	11.08±6.80 SD	45.62±12.25 SD	4.62±2.77 SD
P value	< 0.001	< 0.001	< 0.05	< 0.05

† Data are present as numbers. Maximum and minimum values are shown. Mean and standard deviation are also included. P p values of < 0.05 are considered statistically significant

*APACHE. Acute Physiology and Chronic Health Evaluation

** SOFA. Sequential Organ Failure Assessment (SOFA) score

*** SAPS II. Simplified Acute Physiology Score II

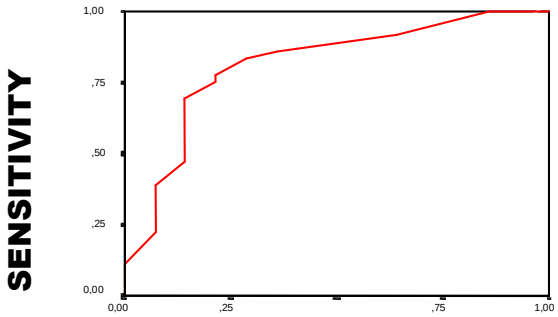
Table 3. Cox Regression model†

Variables	Beta*	P value
Respiratory Failure	2,06	0.001
Number of dysfunctional organs	1,25	0.0002

†Data are presented as numbers. p values of < 0.05 are considered statistically significant
*Beta coefficient

Figure 1

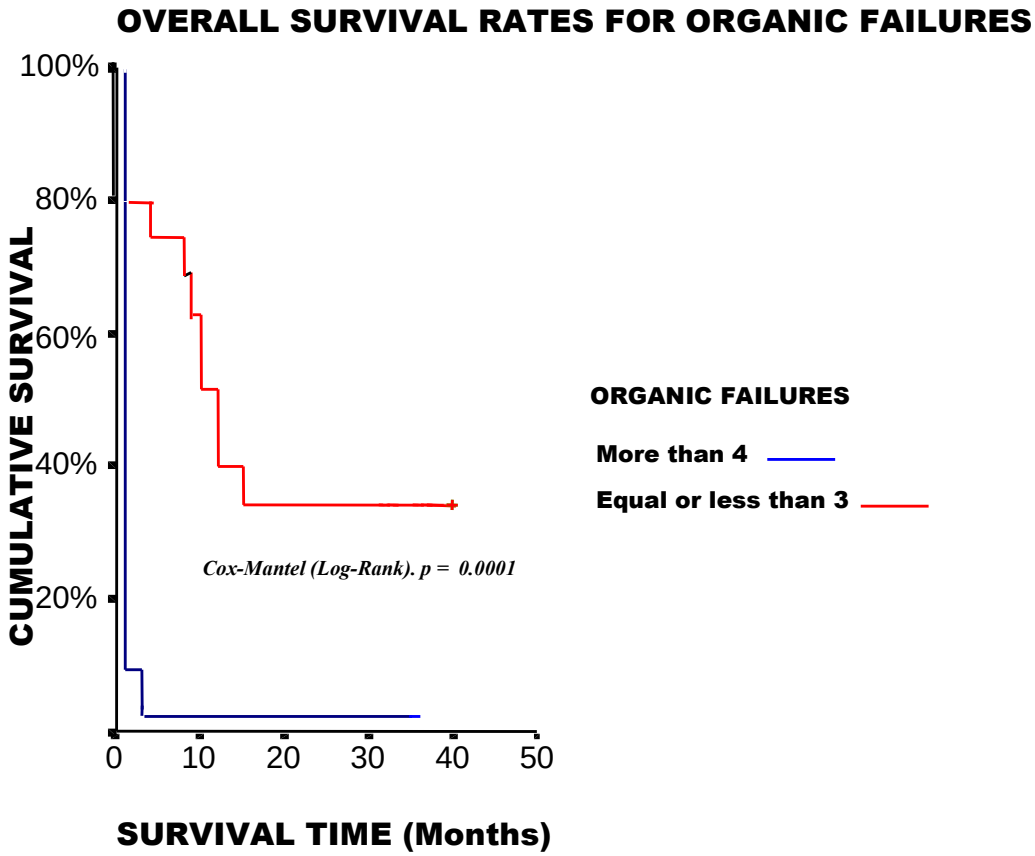
Receiving Operative Curve



*Receiving Operative Curve

ROC 0.90 (CI: 0,81-0,99). SE: 0,45

Figure 2


OVERALL SURVIVAL RATES FOR ORGANIC FAILURES
100%
80%
60%
40%
20%
CUMULATIVE SURVIVAL
0
10
20
30
40
50
SURVIVAL TIME (Months)
Cox-Mantel (Log-Rank). p = 0.0001
ORGANIC FAILURES
More than 4
Equal or less than 3

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