Biological Risk Factors Predict Transfer to Intensive Care Units and Death in Covid-19 Patients

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Abstract

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), causing the COVID-19, has been declared as pandemic by the World Health Organization. Epidemiological and clinical characteristics of patients with COVID-19 have been largely reported but biological risk factors have not yet been well described. In this retrospective and monocentric study, we explored 35 hematological and biochemical parameters, routinely measured at the Amiens University Hospital laboratory, between February 21, 2020 and March 30, 2020 for patients diagnosed with COVID-19. 154 patients were included in this study. We compared biological parameters collected at hospital admission between patients who survived or not after hospitalization. Non survivor patients displayed lower hemoglobin (p=0.02) and bicarbonate concentrations (p=0.03) and higher potassium concentration (p=0.03) compared to the survivors. We then compared these biological parameters between patients hospitalized in conventional care units and patients hospitalized in intensive care units (ICU). Numerous biological examinations had significant variations, including lymphocyte and neutrophil counts, bicarbonate, calcium and C Reactive Protein concentrations. In multivariate Cox analysis, risk factors for aggravation (defined as ICU admission or death) included low bicarbonate levels and hyponatremia. A significant worse overall survival was associated with hyponatremia, hyperkaliemia and prothrombin time > 16.8 seconds. We then proposed a prognostic score, to be validated in a future prospective study. Thus, these biological parameters, easily available, could help clinicians to identify high risk patients at an early stage of infection.

Introduction

In January 2020, Chinese scientists isolated from patients with pneumonia hospitalized in Wuhan city, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) (1) which was renamed in February 2020 coronavirus disease 2019 (COVID-19). Since 11 march 2020, the World Health Organization (WHO) has declared COVID-19 as pandemic. The epidemic began in February in France, near the city of Amiens.

The clinical spectrum of SARS-CoV2 infection is broad, ranging from asymptomatic disease to severe pneumonia with respiratory failure, leading to intensive care unit (ICU) requirement in 14% of the cases and to an overall estimated death rate around 2% (2,3). Many studies have been published recently on epidemiological findings, clinical features and outcomes of patients with SARS-CoV-2 pneumonia (3–5). Among them, a few focused on risk factors of mortality in patients with COVID-19 and identified age, comorbidities and biological parameters such as d-dimer, creatin kinase, high-sensitivity cardiac troponin I, prothrombin time as markers of disease severity (6,7). Nevertheless, most of these reports are limited by the sample size and larger biological studies that aim to identify biological parameters likely to be predictive of transfer to ICU, clinical progression and mortality are still required. We present here the result of a monocentric study based on collection of all biological tests performed routinely in 154 patients hospitalized for COVID-19 between February 21 and March 30, 2020 in the Amiens University Hospital, either in conventional or in intensive care units. This large database allowed us to identify biological markers that were discriminative between favorable *vs.* unfavorable outcomes and between patients that required ICU or not. At a time when hospitals and particularly ICU are at risk of saturation due to a massive

influx of patients, we propose here a score based on simple and routinely available biological tools, that could help to better identify patients who are at higher risk of becoming critically ill and who are most likely to benefit from intensive care treatment.

Material And Methods

Study design and clinical features

This retrospective study included all consecutive adult patients (≥ 18 years old) hospitalized from February 21, 2020 to March 30, 2020 in Amiens hospital and diagnosed with COVID-19 according to the viral detection of SARS-CoV2 with real time polymerase chain reaction (RT- PCR) in our laboratory of virology according to the Pasteur Institute method.

Demographic and biological data were extracted from electronic medical records. Transfer in ICU was effective according to recommandations edicted by the Agence Regionale de Santé Ile-de-France.

Laboratory features were extracted from electronic medical records and checked by hematologist and biochemist physicians. The hematological data collected were: complete blood count (white blood cells (WBC) count, hemoglobin concentration, platelet count) with formula (measurement of neutrophil, eosinophil, basophil, monocyte and lymphocyte counts), coagulation profile (prothrombin time and activated partial thromboplastin time). The biochemical data collected included acide-base balance tests (pH, bicarbonate, base excess, lactate, uric acid, phosphorus), electrolytes (sodium (Na), potassium (K), chlorine (Cl), calcium (Ca)), cardiac (high sensitivity-troponin, myoglobin, B-type Natriuretic Peptide (BNP), creatin kinase (CK)), hepatic (ASAT, ALAT, gamma GT (GGT), bilirubin, lactate dehydrogenase (LDH), alkaline phosphatase), inflammatory (CRP, ferritin), nutritional (albumin and protein), renal tests (urea, creatinin), oxygen saturation and glucose. The results were collected when the patient was admitted at the hospital (day 0).

This study was approved by the institutional review board of Amiens University Hospital (number PI2020_843_0031, 30th March). All methods were carried out in accordance with relevant guidelines and regulations and informed consent was obtained from all subjects.

Statistical analysis

Mean differences between the laboratory parameters from COVID-19 patients were assessed with Student t test.

For survival analyses, all biological parameters were considered as categorical variables, according to physiological range (either normal or abnormal), except for age and creatinin that were considered as continuous variables. Given that creatinine level changes with patients' age and weight, we found that physiological range was not a relevant parameter. Overall Survival (OS) was considered in the whole cohort, and Event Free Survival (EFS, event was defined as transfer to ICU or death) was evaluated only in patients admitted in conventional hospitalization to ensure homogeneity. For categorical variables, OS and

EFS were described using Kaplan-Meier's method in univariate analysis, and the impact on survival analysis was estimated using the log-rank test. For age and creatinine level, the impact on OS and EFS was estimated using a univariate Cox model. Multivariate analysis was performed using a backward Cox regression, computing variables that reached $p<0.1$ significance in univariate analysis.

Results

Patient demographics and baseline characteristics

154 patients were admitted with confirmed SARS-CoV2 infection in the CHU Amiens. These patients were hospitalized in conventional units (n=111, 72%) or ICU (n=43, 28%). Among them, 18 were transferred from conventional care units to ICU. The median age at admission was 77 years (range 23-100), 56% of the patients were male and 44% female. The median follow up was 12 days, ranging 0 to 42 at the time of analysis. The median hospital length of stay in conventional care units and ICU was 12 days. At the time of analysis, 122 patients were alive (79%) and 32 died (21%) from SARS-CoV2 infection.

The baseline characteristics of the patients are summarized in table 1.

Laboratory findings on hospital admission

35 hematological and biochemical parameters routinely measured in the laboratory were retrospectively collected. Characteristics of these analyses performed upon admission to the hospital are summarized in table 2. A small number of tests (<50) was observed for cardiac markers, uric acid, LDH, ferritin and albumin. These tests were then removed from further statistical analysis.

Comparison of laboratory markers between survivor and non-survivor patients

First, we compared the mean levels of the different biological markers in patients who survived (n=122) and patients who died (n=32) from SARS-CoV2 infection (table 3). 4 biological parameters were significantly different between survivors and dead patients, respectively: hemoglobin concentration (12.8 vs 11.9 g/dL, p=0.02), bicarbonate concentration (26.8 vs 25 mmol/L, p=0.03), base excess (0.92 vs -2.11 mmol/L, p=0.02) and potassium concentration (3.96 vs 4.22 mmol/L, p=0.03). We observed a strong trend for lymphocyte count (1.2 vs 0.9 x 10^9/L, p=0.06) and ALAT concentration (50 vs 30 UI/L, p=0.06).

Comparison of laboratory markers between patients hospitalized in conventional and intensive care units

We compared then major laboratory markers between patients hospitalized in conventional care units (n=111) and in ICU (n=43). Results are summarized in table 4. Among the biological parameters, 9 were statistically different between the two groups : white blood cells count (6.8 vs 8.9 x10^9/L, p=0.01), lymphocyte count (1.2 vs 0.8 x10^9/L, p=0.01), neutrophil count (5.2 vs 7.3 x10^9/L , p=0.001), bicarbonate concentration (27. vs 23.7 mmol/L, p<0.001), base excess (1.27 vs -1.87 mmol/L, p=0.003), lactate concentration (1.45 vs 1.99 mmol/L, p=0.015), sodium concentration (138.1 vs 136.2 mmol/L, p=0.01), calcium concentration (2.27 vs 2.12 mmol/L, p<0.001) and C Reactive Protein concentration (82 vs 199.6

mg/L, p<0.001). Furthermore, there was a strong trend for two additional markers : prothrombin time (15 vs 13.48 seconds, p=0.07) and plasma proteins concentration (67.31 vs 64.51 g/L, p=0.052).

Biological markers to identify high risk patients

We performed then survival analyses to determine if biological parameters at diagnosis could predict clinical outcomes. We evaluated OS as risk of death, and EFS, defined as transfer to ICU or death in conventional care units as risk of clinical worsening. Global OS and EFS were described in our cohort by the Kaplan Meier method (figure 1). At median follow up, EFS and OS were around 85%. We then used univariate analysis to evaluate biological parameters for EFS (table 5). We also tested age in as it was described as a powerful risk factor for mortality (6). Lymphopenia (p=0.048), hyponatremia (p=0.003), high uremia levels (p=0.02), hypocalcemia (p=0.01) were statistically significant. In our multivariate model, hyponatremia (p<0.001, HR=11.7 (3.1-44.2)) and low bicarbonate levels (p=0.02, HR=5.4 (1.4-21)) negatively affected EFS. Age was not associated with worse EFS in our study.

For OS, in univariate analysis (table 6), hyponatremia (p=0.038), hyperkaliemia (p=0.005), high creatinine levels (p=0.049), hyperphosphoremia (p=0.006), and O2 saturation (p=0.01) were statistically significant. There was a trend for prolonged prothrombin time > 16,8 seconds (p=0.1). Age was significant in our cohort (p=0.008, HR=1.04 (1.01-1.07)). Then, in our multivariate model (table 6), age (p=0.002, HR=1.13 (1.04-1.22)), prothrombin time > 16,8 seconds (p=0.03, HR=4.62 (1.19-17.94)), hyponatremia (p=0.005, HR=6.99 (1.83-26.72)) and hyperkaliemia (p=0.01, HR=12.1 (1.66-87.75)) were independent prognostic factors.

Proposal prognostic score to predict early survival in COVID-19 patients

Based on the results of the multivariate analysis above, we proposed a simple prognostic score including sodium, potassium and prothrombin time. The calculation of this score is explained in Table 7. Basically, 0, 1 or 2 points are assigned to each of the 3 parameters, according to the weight of their respective HR, resulting in a score ranging from 0 to 6. Using ROC analysis, we proposed that a cut-off of 2 or more predicted a poor prognosis with a sensitivity of 80,7% and a specificity of 93,3% (table 8). Kaplan-Meier survival analysis of patients with the proposal score < or ≥ 2 showed significative difference in early overall survival (Figure 2, p=0,011; HR=0,17; (0.04- 0.67)).

Discussion

In this retrospective study, we aimed to identify relevant biological markers from laboratory examinations, performed routinely in clinical laboratories and thus, easily available. Since the beginning of the pandemic, several studies tried to identify risk factors for mortality and biologic parameters which could screen high-risk from low-risk patients.

We confirmed significant differences previously described between patients hospitalized in ICU and conventional care units like lymphopenia and neutrophilia (3,8). We did not find any difference in platelet counts in all our analyses (9) and prothrombin time reached a statistical significance for OS. Disorders

have been previously reported in coagulation profiles in COVID-10-9 patients (10,11). In our cohort, the non-survivors did not revealed significantly longer PT compared to survivors at admission. However, severely elongated PT was significantly associated with poor prognosis, revealing the potential importance of liver dysfunction and coagulopathy. However, in our study, we did not find significant differences concerning hepatic analyses between the several subgroups of patients, excepting a trend for higher levels of bilirubin in patients hospitalized in ICU. Thus, routine monitoring of hemostasis tests can therefore be useful to monitor the disease progression because some abnormalities (ie, d-dimer greater than 1 µg/mL (6)) are associated with the most severe clinical forms and a risk of increased thrombotic events. ISTH published recently interim guidance for management of coagulopathy in COVID-19 patients, recommending low molecular weight heparin treatment for patients hospitalized with SARS-CoV2 infection (12). Unfortunately, due to the retrospective design, d-dimer was not included in this study because of the small number of tests.

We observed a pejorative role for creatinine and urea in our univariate analysis for OS and for EFS respectively, suggesting the importance of kidney injury in COVID-19 patients. These results are consistent with those of Cheng et al. who showed that patients with kidney disease had a significantly higher risk for in-hospital death (13). Wu et al. also showed a significant difference in urea and creatinine levels in patients with and without Acute Respiratory Distress Syndrome (ARDS) (14). Interestingly, renal failure is frequently associated with hyponatremia and hyperkalemia.

In our study, hyperkaliemia was identified as a risk factor in OS analysis, and hyponatremia was identified as a risk factor in both EFS and OS analysis. To our knowledge, this is the first study to report a prognostic role of these hydro-electrolytic disorders in COVID-19 patients. Hyponatremia may be related to the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and this syndrome frequently occurs in several pulmonary conditions, such as small-cell lung cancer (15). Furthermore, hyponatremia is the most common electrolyte disorder in lung cancer patients and is a well-known prognostic and predictive factor (16). SARS-CoV2 infection may cause SIADH as this virus can target the central nervous system. Though, hyponatremia could be associated with disseminated disease and should be evaluated for every patient at admission.

Hyperkalemia causes heart damage but the small number of cardiac tests performed in this study did not allow us to explore this question. Moreover, one study showed that cardiac impairment in COVID-19 patients was related to the severity of the infection (17).

Based on these results, we proposed a simple and original score based on sodium, potassium and prothrombin time at hospital admission. This proposal score showed that a score ≥ 2 was significantly correlated with a higher risk of mortality with high sensitivity and specificity. However, this proposal score requires validation in a large-scale prospective cohort.

To our knowledge, this is the first study with a dynamic design to evaluate biological markers from laboratory routine examinations.

Our study, however, have some limitations. First, due to the retrospective study design, not all laboratory tests were done in all patients, including lactate dehydrogenase, d-dimer, cardiac analyses or serum ferritin. There were not included in this study, therefore underestimating their predictive role. Second, interpretation of our findings may be limited by the sample size. Last, but not least, a prospective study is necessary to validate our survival datas and our proposal score to identify patients with an increased risk of mortality.

Conclusions

This study allowed us to identify biological risk factors predictive of transfer to ICU and death in Covid-19 patients. We demonstrated the prognostic role of hyponatremia and low bicarbonate levels on ICU transfer and death and the independent value of hyponatremia, hyperkaliemia and PT > 16.8s on OS. We propose then a prognostic score that can be used at an early stage based on these data but which needs to be validated in a prospective cohort. At a time when hospitals are facing a massive influx of patients, early identification of patients at high risk of mortality could improve their outcome with adapted and early intensive care.

Declarations

Competing interests : The authors declare that they have no competing interests

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Tables

Table 1 : Patients characteristics

Characteristics	Covid-19 Patients (n=154)
Age (years)	
Median	77
Min	23
Max	100
Gender(%)	
Male	56
Female	44
Hospitaldepartment	
Hospitalization	111
Intensive care	43
Length of stay in hospital (days)	
Median	12
Min	0
Max	42
Mortality	
Living	122
Dead	32

Table 2 : D0 routine biological parameters of COVID-19 patients

Parameters	Number of patients	Average	Range
Haematology			
WBC ($x10^9$/L)	149	7,16	0,73-19,35
Haemoglobin concentration (g/dL)	149	12,60	7,4-17,4
Platelet count ($x10^9$/L)	150	205,99	58-687
Lymphocyte count ($x10^9$/L)	146	1,11	0,1-12,8
Neutrophil count ($x10^9$/L)	146	5,58	0,6-13,5
PT (s)	122	14.56	10.6-57.9
APTT (ratio)	120	1,18	0,84-4,7
APTT (s)		28.2	19.7-110
Acid-base balance			
pH	81	7,44	7,02-7,57
Bicarbonate (mmol/L)	147	26,45	14,7-35,8
Base excess (mmol/L)	81	0,38	-13,8/ +14
Lactate (mmol/L)	77	1,61	0,7-6,5
Uric acid	7	426,7	132-782
Electrolytes			
Chlorine (mmol/L)	149	101,46	84-113
Sodium (mmol/L)	149	137,81	121-152
Potassium (mmol/L)	149	4,02	2,63-5,58
Calcium (mmol/L)	148	2,25	1,8-2,67
Cardiac analyses			
CK (U/L)	45	2729,8	22-94286
Myoglobin (µg/L)	46	2292,6	11,37-90158
Hs-Troponin (ng/L)	49	76,91	2,96-924,22
BNP (ng/L)	41	191,63	3,5-907,51
Renal analyses			
Creatinine (µmol/L)	147	114,76	36-1181
Urea (mmol/L)	147	8,37	2,3-37
Hepatic analyses			
Alat (U/L)	74	45,18	9-315
Asat (U/L)	74	80,77	10-1646
Total bilirubin (µmol/L)	66	10,94	3-40
LDH (U/L)	11	1009,78	247-5408
Alkaline Ph (U/L)	66	95,68	35-457
gamma GT (U/L)	62	85,53	13-656
Inflammatory analyses			
Ferritin (µg/L)	3	1224,5	569-2408,9
CRP (mg/L)	139	98,34	1,03-44,81
Nutritional analyses			
Albumine (g/L)	9	32,31	28,33-35,23
Plasma proteins (g/L)	147	66,86	46-82
Other biochemical analyses			
Oxygen saturation (%)	81	92,23	31,8-99,6
Glucose (mmol/L)	119	7,26	3,8-22,4
Phosphorus (mmol/L)	147	1,07	0,51-2,77

Table 3 : Comparison of routine biological parameters at D0 of COVID-19 patients in dead versus living COVID19 patients

Parameters	Survivors N=122	Non survivors N=32	p value
Haematology			
WBC ($x10^9$/L)	7,04	7,61	0,39
Haemoglobin concentration (g/dL)	12,78	11,93	**0,02**
Platelet count($x10^9$/L)	202,15	220,71	0,34
Lymphocyte count ($x10^9$/L)	1,17	0,88	0,06
Neutrophil count ($x10^9$/L)	5,43	6,13	0,21
PT (s)	14.14	13.9	0,66
APT T (rati o) APT T (s)	1,18 28.2	1,17 27.8	0,82
Acid-base balance			
pH	7,45	7,40	0,14
Bicarbonate (mmol/L)	26,82	24,99	**0,03**
Basic excess (mmol/L)	0,92	-2,11	**0,02**
Lactate (mmol/L)	1,58	1,77	0,67
Electrolytes			
Chlorine (mmol/L)	101,57	101,06	0,62
Sodium (mmol/L)	138,05	136,87	0,17
Potassium (mmol/L)	3,96	4,22	**0,03**
Calcium (mmol/L)	2,25	2,23	0,68
Renal analyses			
Creatinine (µmol/L)	100,39	170,80	0,11
Urea (mmol/L)	8,10	9,45	0,23
Hepatic analyses			
Alat (U/L)	50,02	30,41	0,06
Asat (U/L)	90,30	51,06	0,26
Total bilirubin (µmol/L)	11,34	9,69	0,39
Alkaline Ph (U/L)	87,98	119,75	0,28
gamma GT (U/L)	80,37	100,38	0,50
Inflammatory analyses			
CRP (mg/L)	102,08	84,43	0,36
Nutritional analyses			
Plasma proteins (g/L)	66,96	66,47	0,69
Other biochemical analyses			
Oxygen saturation (%)	92,67	90,21	0,21
Glucose (mmol/L)	7,29	7,13	0,83
Phosphorus (mmol/L)	1,04	1,18	0,11

Table 4 : Comparison of routine biological parameters at D0 of COVID-19 patients in conventional versus intensive care units

Parameters	Conventional unit N=111	Intensive Care unit N=43	p value
Haematology			
WBC ($x10^9$/L)	6,84	8,88	**0,01**
Haemoglobin concentration (g/dL)	12,68	12,35	0,34
Platelet count ($x10^9$/L)	202,50	222,36	0,27
Lymphocyte count ($x10^9$/L)	1,17	0,81	**0,01**
Neutrophil count ($x10^9$/L)	5,18	7,28	**0,001**
PT (s)	15	13.48	0,07
APTT (ratio) APTT (s)	1,15 29.2	1,28 31.7	0,36
Acid-base balance			
pH	7,44	7,41	0,09
Bicarbonate (mmol/L)	27,02	23,67	**<0,0001**
Base excess (mmol/L)	1,27	-1,87	**0,003**
Lactate (mmol/L)	1,45	1,99	**0,02**
Electrolytes			
Chlorine (mmol/L)	101,59	101,08	0,59
Sodium (mmol/L)	138,14	136,19	**0,013**
Potassium (mmol/L)	4,03	3,90	0,24
Calcium (mmol/L)	2,27	2,12	**<0,0001**
Renal analyses			
Creatinine (µmol/L)	104,47	133,78	0,35
Urea (mmol/L)	7,95	8,73	0,50
Hepatic analyses			
Alat (U/L)	36,00	62,33	0,11
Asat (U/L)	45,91	150,42	0,14
Total bilirubin (µmol/L)	10,19	13,00	0,1
Alkaline Ph (U/L)	96,41	89,89	0,67
gamma GT (U/L)	87,08	69,69	0,37
Inflammatory analyses			
CRP (mg/L)	81,97	199,55	**<0,0001**
Nutritional analyses			
Plasma proteins (g/L)	67,31	64,51	0,052
Other biochemical analyses			
Oxygen saturation (%)	92,56	91,32	0,47
Glucose (mmol/L)	6,94	10,28	0,1
Phosphorus (mmol/L)	1,05	1,07	0,76

Table 5 : Biological risk factors associated with intensive care transfer and death (Event Free Survival : EFS)

Parameters	Univariate Chi-square	P value	Multivariate Chi-square	P value
Age	0.99	0.53		
Haematology				
Lymphocytes <1.5 G/L	3.92	**0.048**		
PNN > 7.5 G./L	2.8	0.09		
Acid-base balance				
Bicarbonate <24 mmol/L	3.36	0.06	**5,4**	**0,02**
Electrolytes				
Sodium > 145 mmol/L	2.9	0.09		
Sodium < 135 mmol/L	8.69	**0.003**	**11.7**	**<0.001**
Potassium < 3.5 mmol/L	2.8	0.09		
Calcium <2.2 mmol/L	6.25	**0.01**		
Renal analyses				
Urea > 8.2 mmol/L	5.56	**0.02**		
Other biochemical analyses				
Oxygen saturation < 92%	2.8	0.09		

Table 6 : Biological risk factors associated with overall survival (OS)

Parameters	Univariate Chi-square/ Hazard ratio	P value	Multivariate Chi-square /Hazard ratio	P value
Age	1,01	**0,008**	1,13	**0,002**
Haematology				
WBC < 4 G/L	4,03	**0,045**		
Hb < 12 g/dL	2,17	0,14		
Lymphocytes <1.5 G/L	2,8	0,09		
PT > 16.8 s	2,6	0,1	4,62	**0,03**
Electrolytes				
Sodium < 135 mmol/L	4,28	**0,038**	6,99	**0,005**
Potassium > 5 mmol/L	7,74	**0,005**	12,1	**0,01**
Renal analyses				
Creatinine > 173 mmol/l	3,86	**0,049**		
Other biochemical analyses				
Oxygen saturation < 92%	6	**0,01**		
Phosphorus >1.45 mmol/L	7,62	**0,006**		

Table 7: Proposal score predictive of survival in COVID19 patients

Parameter	Range	Score point
Sodium (mmol/L)		
	≤130	2
	]130-135]	1
	>135	0
Potassium (mmol/L)		
	≥5,5	2
	]5,5-5]	1
	<5	0
PT (%)		
	≤40	2
	]40-50]	1
	>50	0

Interpretation of the proposal score : Patient at high risk of mortality if score ≥2

Table 8 : Statistical performance of the proposal score

General		
	Area	0,63
	IC Area	0.52-0.75
	p-value	0,011
Cut off≥2		
	Sensibility	80,7 %
	IC Sensibility	62,5-92,6
	Specificity	93,3%
	IC Specificity	87.2-97.0

Figures

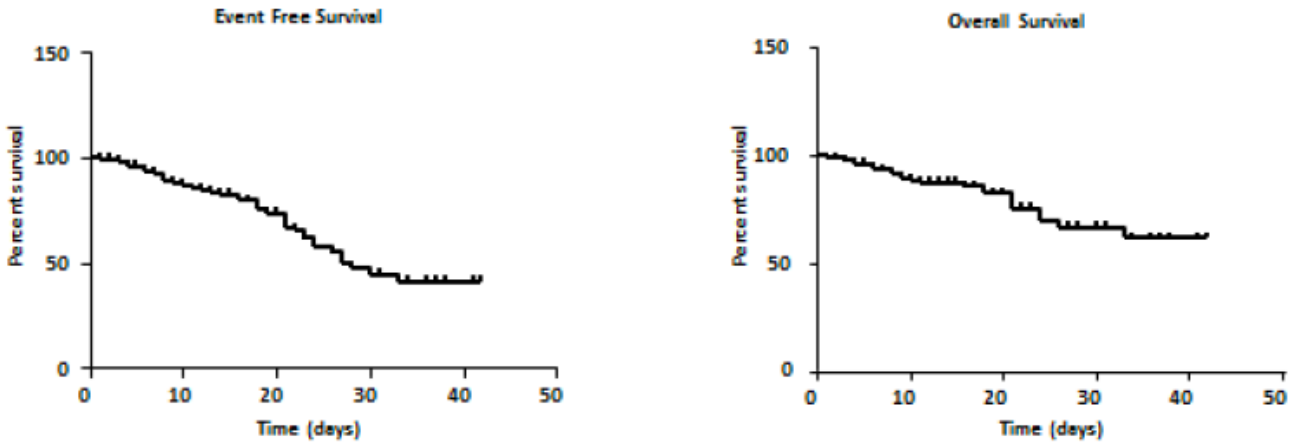

Figure 1

Intensive care transfer as Event Free Survival and Overall Survival in our cohort by the Kaplan Meier method

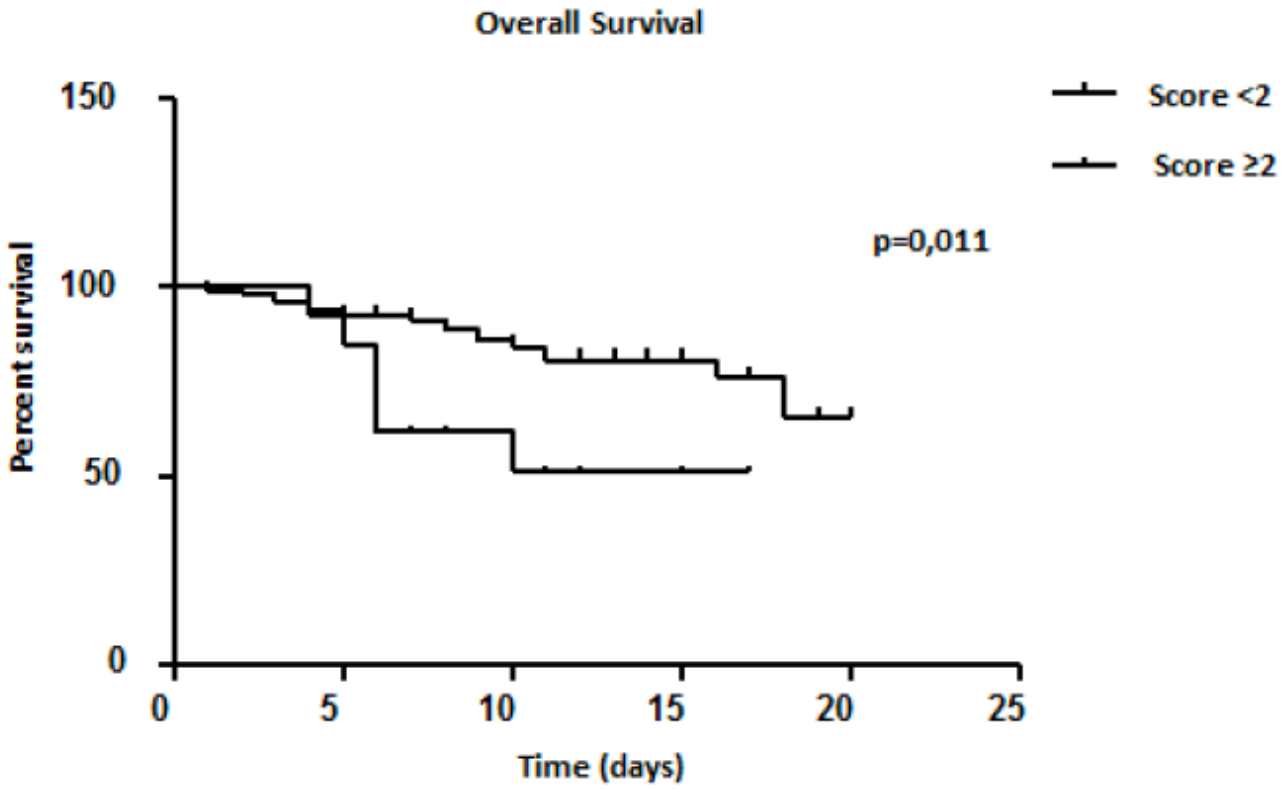

Figure 2

Overall survival according to the proposal score by the Kaplan Meier method