Internal and Emergency Medicine

Natural history and risk stratification of patients undergoing non-invasive ventilation in a non-ICU setting for severe COPD exacerbations

--Manuscript Draft--

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Abstract:	Background and objective. Noninvasive Ventilation (NIV) delivered in an Intensive Care Unit (ICU) has become the cornerstone in the treatment of patients with severe Chronic Obstructive Pulmonary Disease (COPD) exacerbations. A trend towards managing these patients in non-ICU setting has emerged in recent years, although out-of-hospital survival by this approach and how to prognosticate it is unknown. We aimed to investigate these issues.. Methods We consecutively recruited 100 patients (49 males; median age 82 years) who received NIV treatment for acute respiratory failure due to COPD exacerbation in non-ICU medical wards of our hospital, between November 2008 and July 2012. We assessed survival (both in-hospital and out-of-hospital) of all these patients, and analyzed baseline parameters in a Cox proportional hazards model to develop a prognostic score. Results The median survival in the study population was 383 days (240-980). Overall survival

	rates were 71.0, 65.3 and 52.7% at 1, 3 and 12 months respectively. Age >85 years, a history of heart disorders and a neutrophil count ≥10*109 were associated with higher mortality at Cox's analysis ($\chi 2$=35.766, p= 0.0001) and were used to build a prognostic score (NC85). The presence of two or more factors determined the deepest drop in survival (when NC85≥2, mortality at 1, 3 and 12 was 60.7, 70.4 and 77.2% respectively while when NC85=0 were 4.0, 4.0 and 14.0%). Conclusions A simple model, based on three variables (age, neutrophil count and history of heart disease), accurately predicts survival of COPD patients receiving NIV in a non-ICU setting.
Response to Reviewers:	See attachment.

Dear Editor,

We would like to thank you and to the reviewers for the constructive criticism on our article. We extensively revised the manuscript to address the issues raised. Herewith you shall find the point-by-point discussion of the changes we made.

Reviewer n°1

COMMENT ***"First of all the study claims to fill a gap of knowledge and to prognosticate long term outcomes. With a cohort of 100 cases it seems quite ambitious."*** We have rephrased the aim statement, acknowledging that in the previous version it was possibly too ambitious for a single Center cohort. The limited number of patients is mentioned among the study limitations in the discussion section.

COMMENT ***"Second the study criteria for enrollement, how the number of cases to be recruited and the specific of the population to be studied are nebulous."*** We specified further the enrollment criteria in the method section. In our Institution, any patient candidate to receive NIV at our hospital is always evaluated and managed jointly with anesthesiologists; in fact, when the decision to start a NIV is made, the anesthesiologist moves the NIV devices from ICU and sets them at the emergency department or in the ward. The procedure for starting NIV and manage NIV patients has been described in details in the method section. The 100 patients target has been decided on the basis of a sample size calculation that more than 94 patients are needed to find a difference in survival from a 0.6 to 0.4 according to one or more variables with an alpha error of 0.05, and a beta error of 0.2. The details of this sample size analysis have been added to methods section (statistical analysis subsection). Finally, no exclusion criteria was applied since the NIV treatment was decided in clinical practice. This information has been added to the method section for clarity.

COMMENT "*I believe the work would benefit of a significant revision of objectives as well as background premises*." Complying with the suggestions of the reviewer we improved the introduction section maintaining a synthetic approach to comply with the editorial indication of a very short introduction. We maintained the detailed discussion about the literature on the use of NIV outside ICU in the discussion section where it sounds more appropriate. Moreover the objectives of the study have been stated more clearly both in the abstract and in the introduction.

COMMENT "*In the introduction h-ARF is indicated as hyperbaric, however in the methods/results they mentioned about hypoxemic-hyperbaric ARF (please keep consistency)*." Hypercapnic-ARF is the correct definition that we kept in this revised version.

COMMENT "*The cohort seems that was recruited in a manner to stratify the study population in 2 groups, based on gender, but it is not clear then whether this was a prospective randomized study*." If we understand it correctly, the reviewer refers to the fact that, in Table 2, we present the main characteristics of the study population as a whole as well as according to gender. This is only intended to give the reader the information better characterization of the patients we studied, with women (as expected) significantly older than men. This by no means can be interpreted as a study in which patients were randomized according to gender.

COMMENT "*It would be helpful to described the specifics of the ARF at admission, initiation of treatment and whether or not the cohort is different from other hARF (older, sicker, different settings, ventilations, comorbities, age etc etc)*." In this revised version, we explain in greater detail (see Methods) how the decision to start NIV was taken and its practical management. In Table 1 we outlined all clinical and laboratory data when available for all patients, incomplete data were not presented. As suggested we compared our population with available data about features of COPD patients requiring NIV outside ICU in the discussion section. Unfortunately literature on this issue is very scarce.

COMMENT "*Last is the value of the survival analysis (which at the end is the main aim of the report). I believe the study presents interesting points to a real life effectiveness of treatment as well as severity of*

conditions at presentations, but requires significant revisions. The goal is observed mortality, morbidity, survival of a prospective cohort of h-h-ARF managed by NIV in non ICU wards, therefore, background should be better focused on that, methods should consistently report population recruited, methodology of recruitment. Results should not have comments) and present the information of presentations (ABGs, comorb etc), discussion is about survival and history, limitations and final conclusions. We complied with the reviewer's suggestions. We improved background and methods sections, any comment has been removed from the results section, any clinical and laboratory data of the study population available at presentation have been presented in Table 1, discussion has been enhanced in particular in the section dealing with the limitations of the study.

Reviewer n°2

COMMENT "*I have only one question: you talk about cardiac disease, but you do not go down in the details. Right ventricular disease is different from left one, and ischemic disease has a worse prognonsis than hypertensive cardiac disorder. What happens to your study by applying your score in subpopulations of heart disease? maybe you can obtain different results. Please try to do it and discuss in the revision of your MS"*

We included in the "heart disease" category any patient with a previous or actual evidence of heart failure due to any cause as coronary artery disease, chronic arrhythmic disease i.e. atrial fibrillation, valvular disease, right ventricular failure. Due to the data collection methods that relied on clinical reports available at admission, we were not able to retrieve the exact etiology of heart failure for all patients with this comorbidity. In any case the majority of patients had ischemic or valvular heart disease, only 2 patients had precise documentation of cor pulmonale. With these limitations (and numbers) we are not able to stratify mortality according to the etiology of heart disease. A larger, prospective, an ad hoc study is needed to address this question. We commented on this issue in the discussion section.

Reviewer n°3

COMMENT "*While I agree there has been a trend towards managing COPD related h-ARF with NIV, I am not exactly sure how the immediate beneficial effects would transcend to long-term mortality benefit. The long-term mortality would rather be dependent on COPD disease severity and its progression, co-morbid illness and other causes (like cancer, infections). The immediate beneficial effects of NIV are clear, with lesser mortality, lesser chances of nosocomial infections from VAP, ICU related illnesses etc. Hence, it might be interesting to use different adverse prognosticators for immediate morbidity/mortality and another set of adverse prognosticators for long-term mortality"* We performed univariate and multivariate analysis to evaluate if survival at 1 and 3 months were anticipated by different predictors from those resulted to be relevant in the general analysis presented in the manuscript. We did not find any substantial difference: in fact age, the presence of heart disease and neutrophilia were confirmed as predictors for mortality while no other variable was added to the model. These findings can be understood evaluating the Kaplan Maier curve; in fact as the reviewer can notice the greatest drop in survival occurs in the first 90 days (survival drop to 65% in 90 days) while the slope is less steep thereafter. This is also evident in table 4, in fact 77% of patients with negative outcome died in the first 3 months (34/44) and this effect is even more important among patients with 2 or more negative prognostic factors since 86% (19/22) died in the first 3 months and 77% (17/22) in the first month. Since the statistical analysis on survival is strongly influenced by factors that determine the greatest drop in survival, it is evident that the factors that influence the first 90 days survival are more relevant. Additionally, the reviewer should notice that two of the predictor of mortality that entered in our prediction model are features that are not directly related to exacerbation severity but are typical of a frail patient like age and history of heart failure, while the only real predictor of the severity of the exacerbation is neutrophilia. Indeed, patients with the worst short term prognosis (i.e. those with hearth failure, neutrophilia or older age) even if they survive the exacerbation remain at high risk

of death at 1 year, probably for new exacerbation episodes or post hospitalization consequences. Unfortunately, we were not able to retrieve the exact cause of death for all patients at one year, so this explanation remains speculative.

COMMENT *"Page 6 Line 13: Were you able to discern causes of death?":*Since out of hospital mortality has been assessed with phone calls to relatives, we were not able to have a reliable diagnosis of death for all deceased patients. We outlined this in the manuscript at the point indicated by the reviewer.

COMMENT "*Results: Page 7 Line 5: Consider re-framing the sentence. What do you mean by typical of patients admitted to non-ICU wards? Do you have reference*?" We deleted the sentence (see also answers to reviewer 1)

COMMENT "*Page 7 Line 18:It would be useful to know the causes of death at 12 months?* As explained above a reliable cause of death was not available for all patients who deceased.

**COMMENT "*Page 7 Line 26: I would like to make a point on the univariate analysis of various factors tested for survival. There are a total of 17 predictors used to assess the association with survival (50% ~ 50). Biologically why would presence of hypertension lead to death unless the death is deemed to be from CVA, CAD, CKD from uncontrolled hypertension. Similarly, why would CRP, fasting glucose, Sodium level on presentation be a cause of death in 1 year? I would encourage testing predictors, which have mechanistic and biologic relation to outcome, and in our case it would be death.I would also encourage studying factors associated with immediate effects of COPD exacerbation rather that long term mortality which could be related to a wide range of unmeasured factors ranging from disease severity/progression, co-morbid illness contributing to death (like cancer, infection, vascular/cardiac illnesses) as mentioned above*. Our study has been designed to evaluate predictors of survival available at the bedside when the clinician decides to start NIV for a COPD exacerbation. Our study has not been designed to evaluate long term survival in COPD patients. So the variables analyzed are related either to the severity of the clinical condition when the ventilation was started (i.e CRP, fasting glucose etc.) or to brief, easily available, clinical history notes. Therefore, our analysis cannot be divided into a short and long term survival evaluation. Indeed, our study has been designed to predict the prognosis of a patient undergoing to NIV at bedside. So the questions raised by the reviewer cannot be answered with this study design, but will merit an ad hoc study. We outlined these limitations in the discussion section. Additionally, following the reviewer criticisms, hypertension was removed from comorbidities analyzed.

COMMENT "*Discussion: Page 10 Line 1: Moreover, while you evaluate factors like Chronic liver disease against mortality, the number of subjects were just 8 among 100 COPD subjects. In a 2 by 2 table, low numbers (cell count less than 5) would spurious results.* Following the reviewer's suggestion, chronic liver disease has been removed from the list of comorbidities analyzed, due to the scarce number of patients.

Title Page

TITLE:

Natural history and risk stratification of patients undergoing non-invasive ventilation in a non-ICU setting for severe COPD exacerbations

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ABSTRACT

Background and objective.

Noninvasive Ventilation (NIV) delivered in an Intensive Care Unit (ICU) has become the cornerstone in the treatment of patients with severe Chronic Obstructive Pulmonary Disease (COPD) exacerbations. A trend towards managing these patients in non-ICU setting has emerged in recent years, although out-of-hospital survival by this approach and how to prognosticate it is unknown. We aimed to investigate these issues..

Methods

We consecutively recruited 100 patients (49 males; median age 82 years) who received NIV treatment for acute respiratory failure due to COPD exacerbation in non-ICU medical wards of our hospital, between November 2008 and July 2012. We assessed survival (both in-hospital and out-of-hospital) of all these patients, and analyzed baseline parameters in a Cox proportional hazards model to develop a prognostic score.

Results

The median survival in the study population was 383 days (240-980). Overall survival rates were 71.0, 65.3 and 52.7% at 1, 3 and 12 months respectively. Age >85 years, a history of heart disorders and a neutrophil count $\geq 10*10^9$ were associated with higher mortality at Cox's analysis ($\chi 2=35.766$, $p= 0.0001$), and were used to build a prognostic score (NC85). The presence of two or more factors determined the deepest drop in survival (when NC85≥2, mortality at 1, 3 and 12 was 60.7, 70.4 and 77.2% respectively while when NC85=0 were 4.0, 4.0 and 14.0%).

Conclusions

A simple model, based on three variables (age, neutrophil count and history of heart disease), accurately predicts survival of COPD patients receiving NIV in a non-ICU setting.

Keywords

Non-invasive ventilation

COPD exacerbations

Non-ICU setting

Risk stratification

Introduction

In the last decades, the intermittent application of noninvasive ventilation (NIV) has proved to be effective in decreasing intubation rate and mortality of patients with hypercapnic acute respiratory failure (h-ARF) due to chronic obstructive pulmonary disease (COPD) exacerbations [1,2]**.** In these patients, early NIV to prevent further deterioration results in improved outcomes, compared to late NIV use in alternative to invasive ventilation [3]. To allow its earlier and broader use and when permitted by patient's condition, NIV is now often applied in general wards [4, 5]. This approach is particularly appealing when Intensive Care Unit (ICU) beds are scarce and for patients who, because of age or comorbidities, are not candidates for invasive ventilation in the ICU. Specifically, among patients with acute exacerbations of COPD causing h-ARF, on ward NIV proves d to be feasible and effective [6], able to improve patient outcomes in selected patients with mild to moderate h-ARF [7], and applicable even in rural hospitals with no ICU [8].

Despite the expanded use of in ward NIV to treat h-ARF, no study has so far evaluated the long-term outcomes (including out-of-hospital survival) or has identified prognostic factors for these patient. A better insight on these factors might be helpful to devise better strategies to manage high-risk patients and improve survival.

We designed the present study, including COPD patients who received NIV for in ward treatment of h-ARF, with the aim of evaluating survival and to search for predictors easily available at the time of patient amission.

Methods

Study population

We retrieved data of all patients consecutively admitted to non-ICU medical wards of a university hospital who required NIV treatment for hypercapnic ARF because of COPD exacerbation between November 2008 and July 2012. Hypercapnic ARF was defined either with or without severe respiratory acidosis (pH <7.35) or with hypoxemia (PaO_2 <60 mmHg) if $PaCO_2$ >45 mmHg. COPD exacerbation was defined according to GOLD guidelines [9] as an acute event characterized by worsening of the patient's respiratory symptoms beyond normal day-to-day variations and leading to a change in medication.

No exclusion criteria were applied since the NIV treatment was decided in clinical practice. When ventilation support was considered, the anaesthesiologist was called for consultation either by emergency department or non-ICU ward physicians; if the criteria for NIV support were met, the anaesthesiologist set the NIV device. Thereafter, vital signs and blood gas analysis were monitored in the following hours/day to evaluate the efficacy of treatment.

The patients were selected from an electronic database where all patients who received NIV at our institution were recorded prospectively from November 1, 2008 to July 31, 2012. Patients' data were recorded according to local ethical guidelines.

Data collection

The following data were collected for subjects included in the analysis:

- Demographic data: age and gender;
- Previous COPD history: current treatment upon hospital admission (including domiciliary oxygen therapy), duration of disease, previous anti-pneumococcal and flu vaccine administration, functional lung tests if performed in the last 12 months.
- Comorbidities: heart disease (any previous event or actual evidence of heart failure due to any cause as coronary artery disease chronic dysrhythmic disease i.e. atrial

fibrillation, valvular disease, right ventricular failure), Type 2 Diabetes Mellitus, chronic liver disease, arterial hypertension and chronic renal failure;

- The following laboratory data were collected at the time of hospital admission: complete blood cells count, arterial blood gas, glucose plasma concentration, C-reactive Protein, creatinine, liver function tests. All assays were carried out in our central laboratory, for clinical purpose;
- Chest X-Ray Study;
- NIV parameters: time and setting of ventilators; all patients were treated with a full-face device;

Survival data were collected by consulting clinical records, discharge letters and phone call to patients or relatives. Causes of death were not available for all deceased patients.

Statistical Analysis

The collected data have been analyzed by the statistical software MedCalc, Version 12.7.0.0 (MedCalc Software, Broekstraat 52, 9030 Mariakerke, Belgium). Continuous variables are presented as medians (Confidence Interval 95%, 95%CI). Categorical variables are presented as frequencies (percentage); the association between categorical variables was analysed by the chi square for trend test.

Survival is time from hospital admission to death; Kaplan-Meier curves have been used to display survival data. Hazard ratios (CI95%) were calculated for each potential predictor of death. The log-rank test was used to verify differences in survival probability between groups. Finally, the Cox proportional hazard model with a stepwise approach has been used to analyse the weight of survival predictors and build a prognostic score. The level of statistical significance for all statistical tests was 0.05 (two-tailed). A population size of more than 94

subjects was needed to find a 0.2 difference in survival according to one variable with an alpha error of 0.05, and a beta error of 0.2.

Results

Table 1 displays the main clinical and demographic features of the study population. Median age was 82 years (95%CI 75-87), severe COPD disease was highly prevalent (62.0% patients) and comorbidities were common (in particular, 40.0% have chronic heart disease).

The median survival was 383 days (95%CI 240-980). Figure 1 shows the probability of survival of patients over time, estimated by Kaplan-Meier analysis. Overall survival was 71.0, 65.3 and 52.7% at 1, 3 and 12 months respectively. In-hospital mortality was 27.0%. There were no significant differences in survival between males and females (median survival was 398 for males and 383 for females, Logrank test p=0.775)

Table 2 displays the influence of several variables on patients' survival at univariate analysis. An age ≥85 years, a history of heart disorders, a white blood cell (WBC) count $\geq 12\times10^9$ and a neutrophil count $\geq 10\times10^9$ all affected survival. Kaplan-Meier survival estimates according to these four variables are presented in Figure 2.

In table 3 the results of Cox proportional hazards regression analysis are summarized ($\chi 2=35.8$, p= 0.0001). All variables except the WBC count fitted the stepwise model. On the basis of this analysis a prognostic score was prepared, named NC85 for easy recall (Neutrophil count, cardiac disease, Age ≥85 years). As evident from the figure 3, the higher the number of negative prognostic factors, the lower is the survival rate. The cumulative survival rate at 1, 3 and 12 months according to the number of prognostic factors present is shown in table 4. The presence of two or more factors was associated with the deepest drop in survival.

Discussion

The present study shows that the mid-term prognosis of patients who receive NIV in a non-ICU setting is dim, almost half of these patients being dead after one year, and suggests that survival can be predicted easily by simple parameters always available at baseline. These findings need to be discussed at the light of the knowledge provided by the literature on NIV, and of the ethical and economic issues currently facing western countries with an aging population and a high prevalence of COPD.

Fifteen years ago, a large randomized trial showed that NIV in a non-ICU setting is safe and effective; with significantly reduced intubation rates, lower in-hospital mortality, quicker pH improvement in the first hour and greater fall in the respiratory rate at 4 h as compared to standard treatment [7]. Based on these excellent short-term results and despite the paucity of data on out-of-hospital survival, the use of NIV outside of the ICU has gained widespread popularity, fuelled by the need of dealing with a substantial number of elderly patients with acute heart failure or severe COPD exacerbation. Here, we focused on the latter condition, hoping that a better knowledge of the natural history after an acute COPD exacerbation requiring NIV might help in devising strategies to improve mid-term survival of these very fragile patients.

The median survival of our study population was 383 days, with 52.7% surviving 12 months or longer, with no significant gender differences. Our results show a slightly worse prognosis than expected according to GOLD 2015 describing a 1-year survival rate of 55-60% of patients who undergo mechanical ventilation. The reason for this difference is likely attributable to differences in the demographic and clinical features of our study population; in fact, previous papers reporting a lower mortality have been conducted on significantly younger patients [7, 10, 11] or those affected by a first exacerbation [12]. We studied patients whose profile can be considered typical of a medical ward for acute conditions: old (median

age 82 years, with many patients belonging to the “oldest old” category), frail, suffering from multiple illnesses, often with a history of multiple exacerbations. We also observed a high short-term mortality (27.0% in-hospital, 29.0% at 1-month), worse than that recently reported by Fiorino et al. [8] in a similar cohort of COPD patients with acute respiratory failure (18%). This difference can be explained by the different selection criteria, since in that paper several different causes of ARF were included, COPD exacerbation being the cause of ARF only in 40% of cases. On the contrary we included only COPD exacerbation, which is generally more severe.

Our data show – not surprisingly – that patients aged >85 years have a significantly worse prognosis in comparison to younger patients requiring NIV. Age, of course, is expected to be a very strong predictor of mortality, and its role as a risk factor is in line with previous reports [12]. The line might need to be drawn on a fairly high level, though, since categorizing patients as ≤ 75 years and> 75 years the log-rank test loses statistical significance, though maintaining a trend (data not shown).

Considering laboratory variables, both total WBC and neutrophil counts at admission are associated with survival at univariate analysis. The two values are closely related to each other (the neutrophils normally being the major component of the white blood cell count), and is thus not surprising that at multivariate analysis only one (the neutrophil count) prevails. The potential prognostic value of the neutrophil count has already been associated with the prognosis of other acute conditions such as STEMI (ST-Elevation Myocardial Infarction) [13], infective endocarditis [14], surgical procedures [15], and is in agreement with earlier data on the mortality of patients with COPD [16]. Interestingly, progression of COPD is known to be associated with the accumulation of polymorphonuclear neutrophils in the lumen of the small airways, coupled to a repair or remodeling process that thickens the walls of these airways. [17].

We further evaluated the prognostic value of comorbidities, especially those commonly associated with COPD: heart disease and chronic renal failure. Only the presence of heart disease was statistically associated with a significant reduction in life expectancy. This confirms what has long been known about the role played by the disease on cardiovascular mortality in patients with COPD [18]. Due to the data collection methods that relied on clinical reports available at admission, we were not able to retrieve the exact etiology of heart failure for all patients. Therefore, we cannot stratify mortality according to the etiology of heart disease. Based on age at admission, neutrophil count and history of heart disease, a simple prognostic score can be built (we propose to call it NC85), to facilitate its recall. Mortality at 1 and 3 months varies from 60.7 to 70.4% in the presence of two or more NC85 factors, while it is only 4% in the presence of 0/3 unfavourable factors; at one year, the corresponding figures are 77.2 and 14.0%. Due to its simplicity, the NC85 score would be very user-friendly at the bedside, which is essential in everyday clinical practice.

Our study has of course several limitations: the specifics of the study population might have led us to overestimate the mortality of COPD exacerbations in comparison to other series, however we believe our study portrays a true picture of what happens in non-ICU medical wards today. The single centre enrolled population of 100 patients may have led to underestimation of the contributions of some variables. Our study has been designed to estimate survival based on clinical and laboratory variables available at the time the decision to start NIV is made. So we were not able to include in the analysis several other predictors of long term mortality such as cancer or infections. With these limitations, this study cannot evaluate all variables that may influence long term survival of COPD patients. However, it may help the clinician to gain a glimpse of the patient's fate in and out of hospital when NIV is started for a COPD exacerbation.

Conclusions

Our study documents that around half of COPD patients undergoing NIV for type II respiratory failure (hypoxemic hypercapnic) in a non-ICU ward will not survive one year from the day of admission. However, there is significant variability in the survival probabilities of these patients, captured by three simple variables, almost always known to the presentation: age, polymorphonuclear count and history of heart disease. Correct risk stratification of these patients might be instrumental in devising strategies for better in- and out-of-hospital management of these very sick and frail patients.

Conflict of Interest.

The authors declare that they have no conflict of interest.

Ethical approval.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

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Tables

Table 1. Clinical and demographic features of the study population. Abbreviations: ARF, Acute Respiratory Failure; NIV, Non-Invasive Pressure Support Ventilation; CRP, C-Reactive Protein; WBC, White Blood Cells.

	Total N. = 100	Males N.= 49	Females N.= 51	p
Age, years	82 (75.0-87.0)	80 (73.0-86.0)	84 (77.0-88.0)	**0.024**
Hospital admission in the previous 3 months, N.	24	14	10	0.353
Antibiotic treatment in the previous 3 months, N.	21	10	11	1.000
Domiciliary oxygen therapy, No vs. Yes	38/62	18/31	20/31	1.000
NIV duration, hs.	72 (48-120)	72 (48-96)	72 (48-144)	0.408
History of heart disease, N.	40	21	19	0.840
Chronic renal failure, N.	29	13	16	0.662
CRP, mg/L	5.02 (1.66-12.47)	5.53 (2.62-14.43)	2.78 (1.38-11.15)	0.079
Fasting Plasma Glucose, mg/dl	151 (121-182)	151 (118.5-179)	145 (123-183)	0.762
pH	7.27 (7.19-7.31)	7.27 (7.20-7.31)	7.24 (7.19-7.31)	0.397
$PaCO_2$, mm Hg	75.0 (65.0-91.0)	72.0 (61.1-91.5)	76.5 (67.0-90.4)	0.310
Na, mmol/L	138 (136-143)	138 (136-143)	138 (136-143)	0.815
Hematocrit, %	41.0 (36.1-45.8)	41.0 (36.5-46.7)	39.7 (35.3-44.3)	0.242
WBC count, $\times 10^9$/L	10.5 (8.4-13.8)	10.8 (8.6-14.3)	10.4 (7.9-13.5)	0.287
Neutrophils count, $\times 10^9$/L	8.1 (6.3-10.8)	8.9 (6.7-11.0)	7.7 (5.5-10.1)	0.119

Table 2. Effect of analyzed variables on survival. Abbreviations: ARF, Acute Respiratory Failure; NIV, Non-Invasive Pressure Support Ventilation; CRP, C-Reactive Protein; WBC, White Blood Cells.

Variables	Hazard ratio	95%CI
Age, years (> 85 vs. ≤ 85)	**2.50**	**1.38-4.50**
Hospital admission in the previous 3 months, N.	1.46	0.75-2.82
Antibiotic treatment in the previous 3 months, N.	1.18	0.60-2.32
Domiciliary oxygen therapy, Yes vs. No	1.30	0.74-2.26
NIV duration, h (≤ 72 vs. > 72)	1.02	0.59-1.77
History of heart failure, Yes vs. No	**1.90**	**1.06-3.37**
Chronic renal failure, Yes vs. No	1.21	0.66-2.21
CRP, mg/L (> 10 vs. ≤ 10)	1.05	0.56-1.99
Fasting plasma glucose, mg/dl (≤ 180 vs. > 180)	0.78	0.42-1.45
pH (> 7.24 vs. ≤ 7.24)	0.83	0.48-1.44
$PaCO_2$, mmHg (≤ 80 vs. > 80)	0.67	0.38-1.15
Na, mmol/L (≤ 134 vs. > 134) (≤ 144 vs. > 144)	 0.89 1.25	 0.45-1.73 0.52-2.99
Hematocrit, % (≤ 45 vs. > 45)	0.57	0.31-1.04
WBC count, $\times 10^9$/L (> 12 vs. ≤ 12)	**2.03**	**1.14-3.63**
Neutrophils count, $\times 10^9$/L (> 10 vs. ≤ 10)	**2.45**	**1.30-4.62**

Table 3. Summary of multivariate survival analysis (Cox proportional hazards regression with a stepwise approach). Abbreviations: HR, hazard ratio; 95%CI, 95% confidence interval; WBC, white blood cell.

Covariates	HR	95%CI	p
Age >85 years	4.1480	2.2838-7.5338	**<0.0001**
Neutrophils, > 10×10^9/L	3.3665	1.8738-6.0484	**0.0001**
History of heart disease	2.3292	1.3219-4.1042	**0.0036**
WBC count, > 12×10^9/L	Not included in the model		

Table 4. Survival rates according to the NC85 prognostic index.

SURVIVAL	**NUMBER OF PROGNOSTIC FACTORS PRESENT (NC85)**			**OVERALL SURVIVAL**	(χ^2 trend, p)
	0	**1**	**2**		
1 month survival %, n. at risk, n. deceased	96.0%, 25, 1	76.6%, 47, 11	39.3%, 28, 17	71.0%, 100, 29	**21.013, p=0.0001**
3 month survival %, n. at risk, n. deceased	96.0%, 25, 1	69.6%, 46, 14	29.6%, 27, 19	65.3%, 98, 34	**24.441, p=0.0001**
12 month survival %, n. at risk, n. deceased	86.0%, 21.5, 3	55.1%, 44.5, 20	22.8%, 28.5, 22	52.7%, 93, 44	**19.678, p=0.0001**

Figure legends.

Figure 1: Overall survival of the study population. Number of events = 53, number censored: = 47, median survival: 383 days, 95% CI for the median 240 to 980.

Figure 2: Kaplan-Meier curves, stratified according to variables associated with survival at univariate analysis (logrank test). Top left; history of heart disease (Chi-squared 5.7520, p=0.0165), top right age≥85 years (Chi-squared 12.2441, p=0.0005), bottom left WBC count, $\times 10^9$/L ≥12 (Chi-squared 7.1481, p=0.0075), bottom right Neutrophils count, 10^9/L ≥10 (Chi-squared 11.4379, p=0.0007).

Figure 3. Kaplan-Meier curves, stratified according to different NC85 scores. The continuous line represents patients with NC85 score = 0, the dashed line patients with NC85 score = 1, and the dotted line patients with NC85 ≥ 2. Statistical significance was assessed by means of the logrank test (Chi-squared for trend: 27.2128, p = 0.0001).

Figure 1

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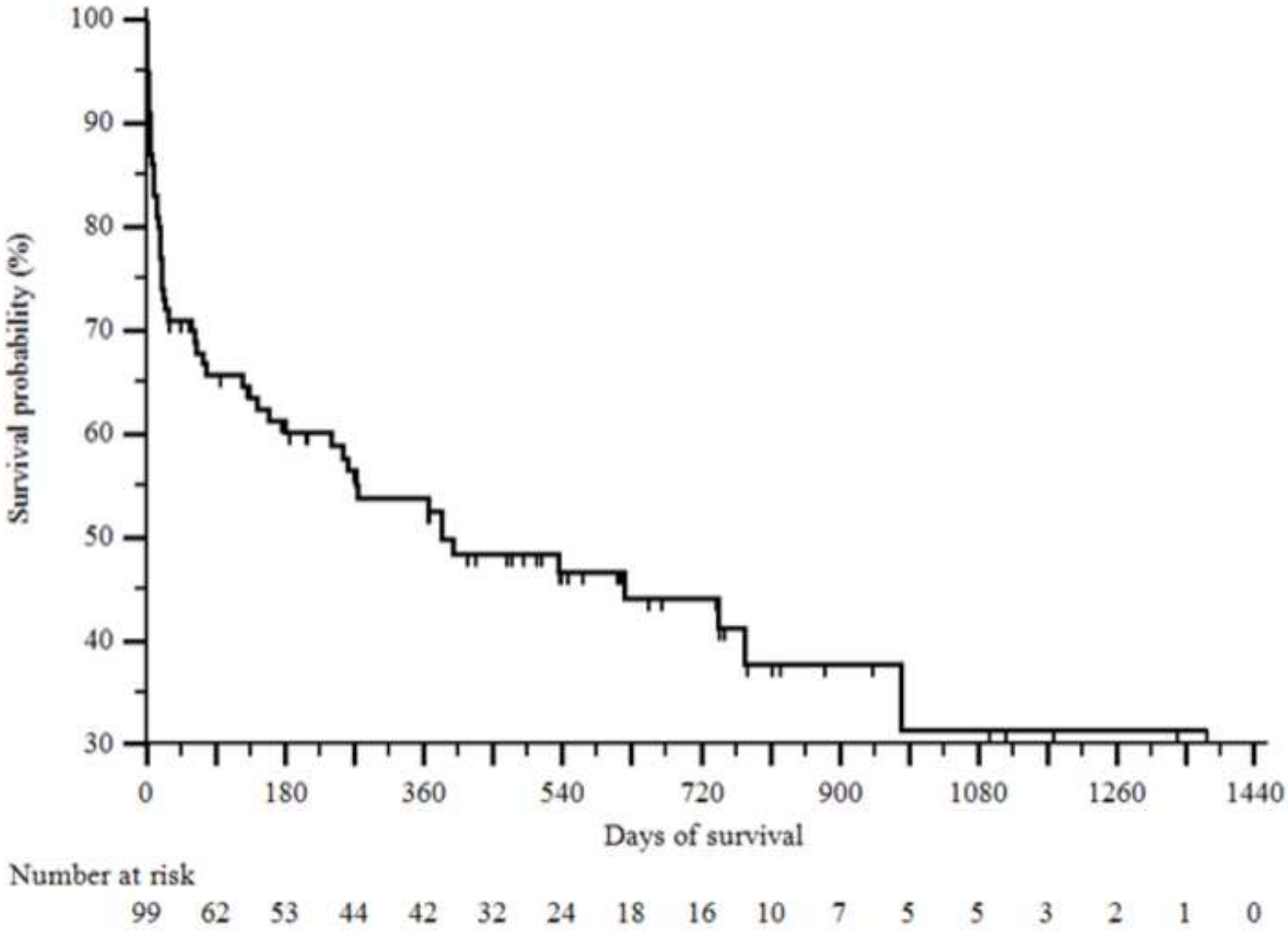

Figure 2

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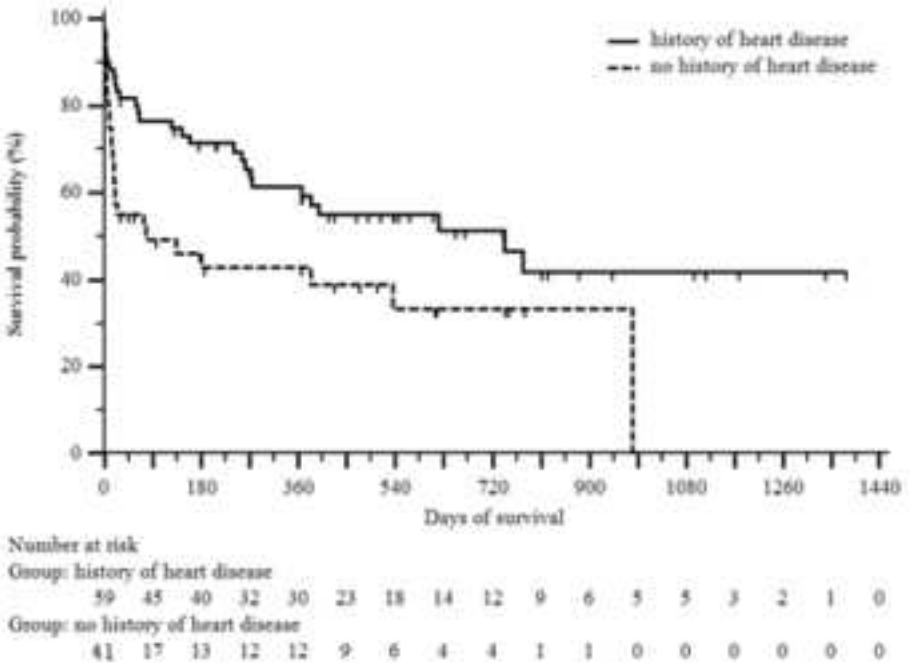

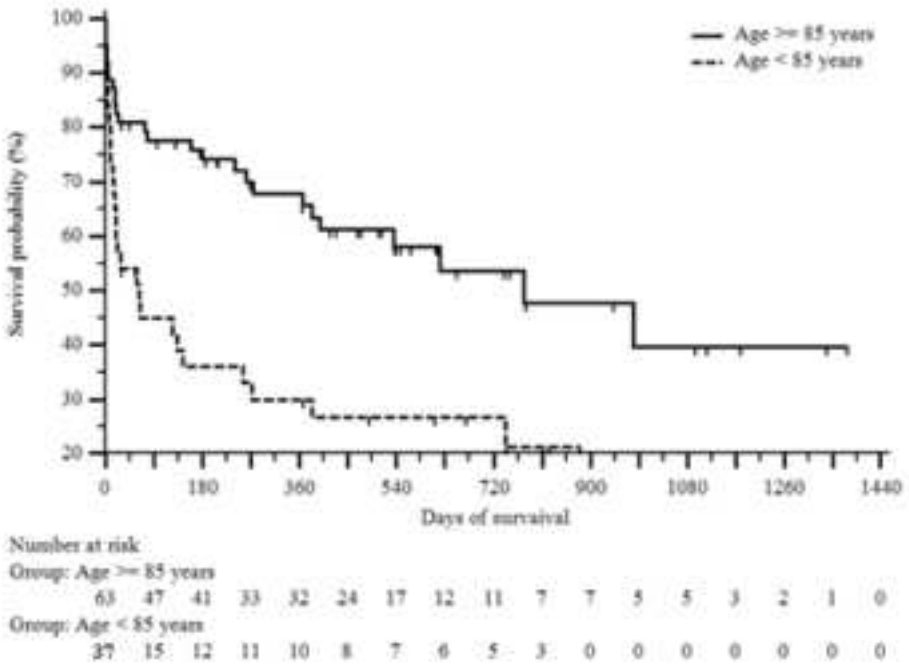

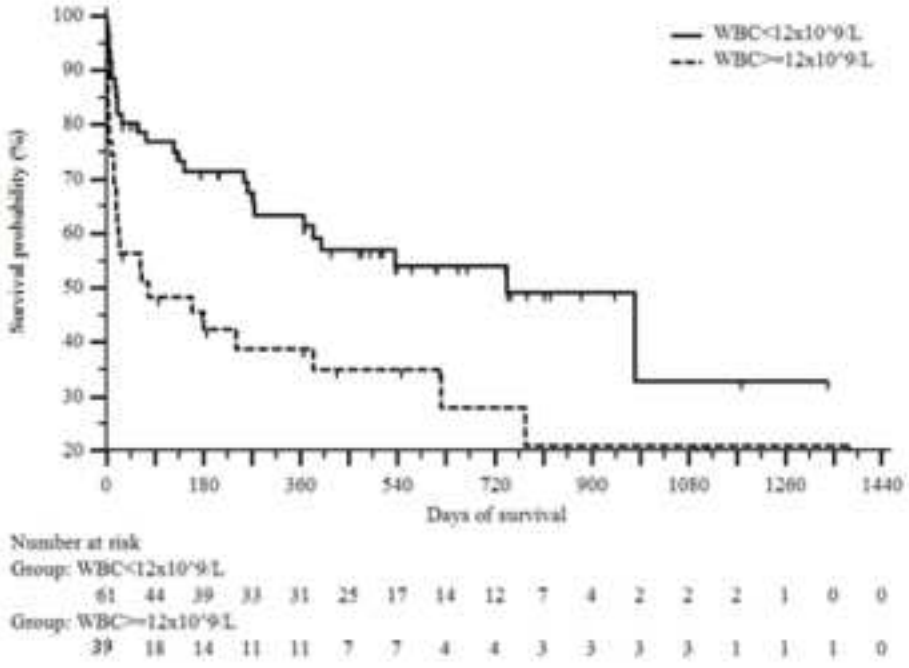

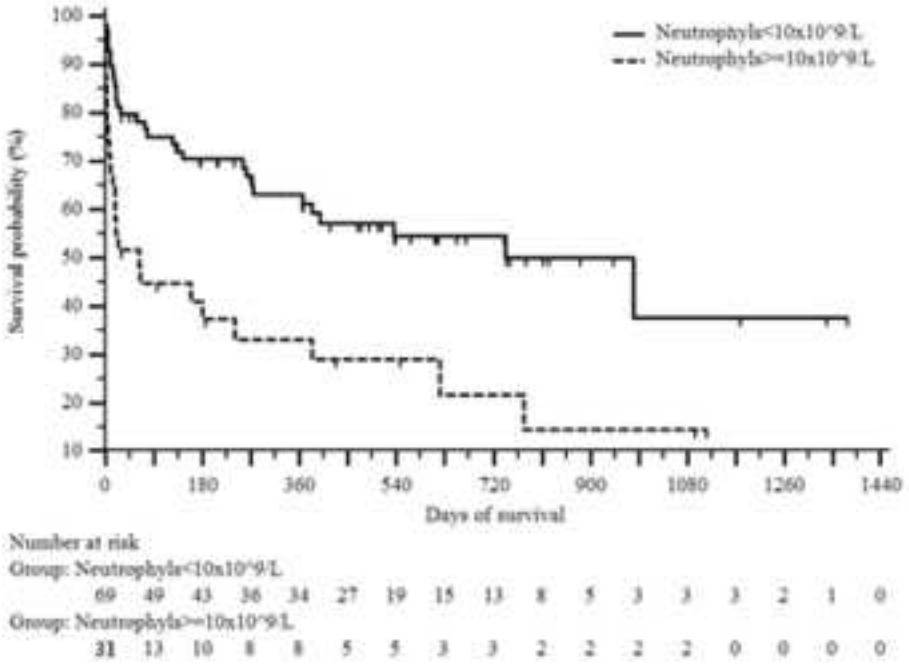

Figure 3

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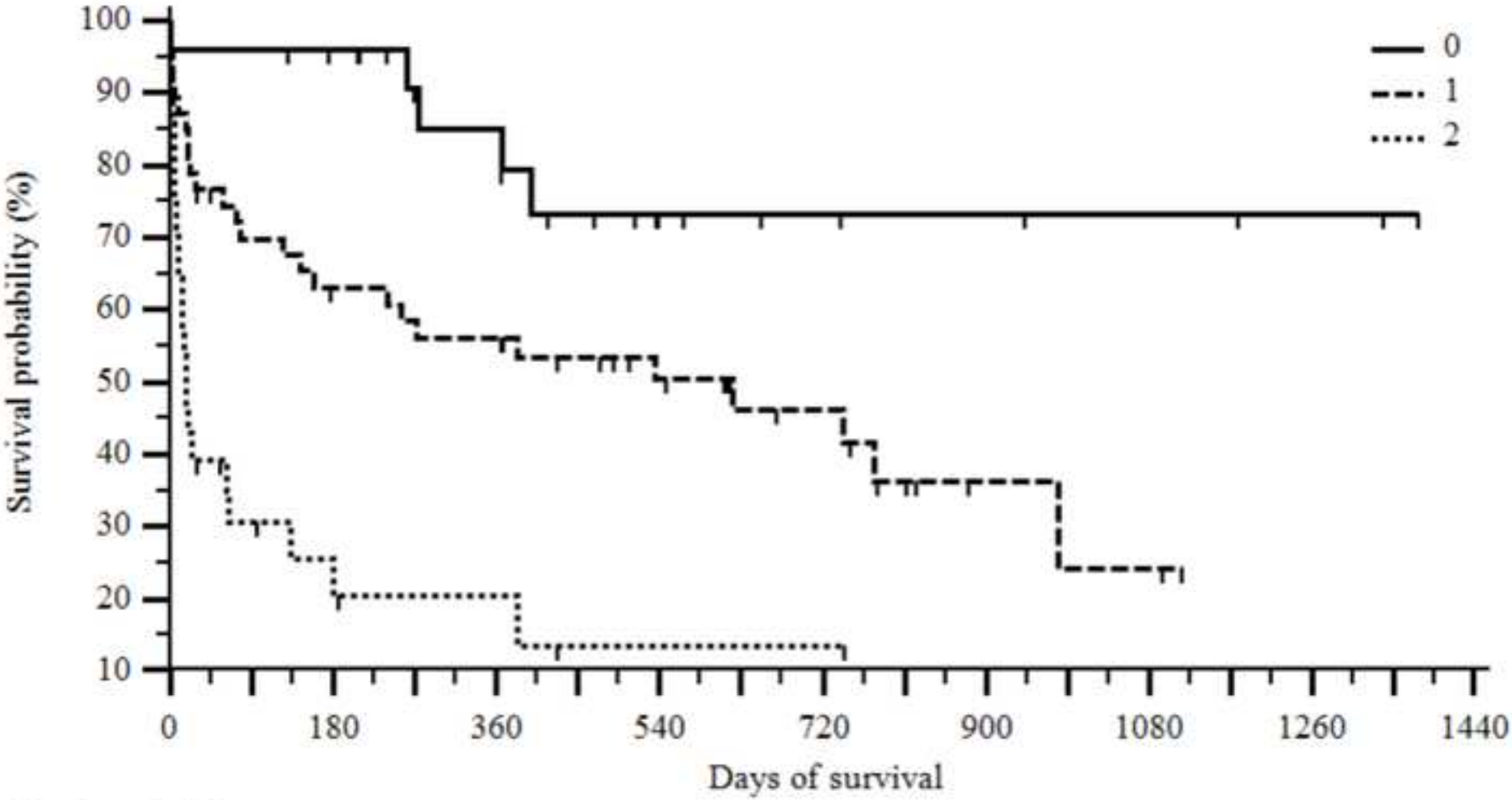

Number at risk

Group: 0	**26**	24	22	16	15	11	7	6	5	4	4	3	3	3	2	1	0
Group: 1	47	31	27	25	24	20	16	11	10	6	3	2	2	0	0	0	0
Group: 2	27	7	4	3	3	1	1	1	1	0	0	0	0	0	0	0	0

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