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RISK FACTORS' IDENTIFICATION ACCORDING TO THE DEVELOPMENT OF HEALTHCARE ASSOCIATED INFECTIONS AND MORTALITY BY USING COMPETING MODELS AT TIMONE UNIVERSITY HOSPITAL'S ICU

Ahmed. Haddadi, MA, PhD
Research Unit EA 2694 Public health, epidemiology and quality of care, Medical university Lille2
Mohamed. Lemdani, PU
Research Unit EA 2694 Public health, epidemiology and quality of care, Biostatistics laboratory, Faculty of Pharmacy ; university Lille2
Hervet. Hubert, PU
Research Unit EA 2694 Public health, epidemiology and quality of care, Institute of Public Health; university Lille2

Abstract

Whatever their specialty (surgical, medical or both), intensive care units have to take care of patients due to life-threatening conditions as the result of one or even several organ failures. They register the highest mortality rates (Sheng WH, 2005), and the highest numbers of nosocomial infections (Mathieu LM, 2001). There have been numerous studies intended to evaluate the risk factors and the consequences of these infections in ICU (Intensive Care Unit) patients. However the analyses in most of these studies disregard the fact that there are additional competing events such as discharge or death. The study is retrospective. It is based on a total of 250 patients of at least 16 years old and having spent at least 72 hours in ICU in the Timone University Hospital. Several risk factors were studied in two distinct competitive risk models. In the first model, we investigated the nosocomial infections risk factors with such a competing risk model as discharge (patients dead or living). The mortality risk factors were studied in the second model in which the patient being discharged faces the mortality competing risk. 46 patients developed at least one nosocomial episode, and 65 died. The nosocomial infection objectified risk factors are: CVC (cause-specific hazard ratio = 9.08; 95% CI 1.10 to 75.20), chronic renal failure (8.99; 95% CI 1.92 to 42.12) and tracheotomy (2.69; 95% CI 1.45 to 5.01). Cancer (2.69; 95% CI 1.48 to 4.89), transplant (7.30; 95% CI 1.83 to 29.19)

and the SOFA score (1.36; 95% CI 1.23 to 1.51) are the target factors for mortality risk. Of all the documented scores in the present study the SOFA is the score with the highest predictive capacity as far as death risk is concerned. On the other hand, even if the nosocomial infection alters the event discharge, its impact on mortality is not completely established

Keywords: Intensive care, risk factors, nosocomial Infections, ICU-mortality, competing risks models

Introduction

Hospital acquired infection are a major and consequential health problem because of their frequency, their cost and their gravity (Sheng WH, 2005), (Mathieu LM, 2001), (Ahmed HADDADI, 2013).

The efficiency's control study of nosocomial infections led in the USA count around 2.1 million nosocomial events out of a total of 37.7 million admissions in a year. According to the results of the same study the death rate due to nosocomial infections is 77, 000 (Ahmed HADDADI, 2013), (Haley RW, 1985), (Archibald LK, 2007).

Though the origins of the health care associated infections are similar, ICUs count prevalence rates two to five times higher than in other health care services. Indeed, according to (Digiovine B, 1999) 31.5% to 82.4% of the patients may develop bacteraemia in ICU.

These high rates can be mainly explained by the elaborateness of the pathologies, the therapeutic and/or diagnostic procedures, often invasive, that they require.

The nosocomial event would be the result of the morbid interaction of pathogenic agents, healthcare and vulnerability of the patients. Thus, it may be due of a complex relationship between several factors (Wenzel R. P. Thompson, 1983).

Amidst those factors, the studies (Sheng WH, 2005), (Ahmed HADDADI, 2013). (Archibald LK, 2007), (Wenzel R. P. Thompson, 1983), (Vincent JL, 2003), (Cevik MA, 2005), (Girou E, 1998), (Richards MJ, 2000) quote the use of invasive devices, induced immunodepletion or secondary to acute pathology, the relatively advanced age of the patients, the associated chronic pathologies, antibiotherapy and multi-resistant bacteria.

The studies (Esen S, 2004), (Craven DE, 1988), (Ponce de León-Rosales SP, 2000), (Vincent JL, 2003), (Richards MJ, 1999) prove a significant association between nosocomial infection rates and the length of stay and, *de facto,* an increase of the cost. On the other hand, though it is difficult to establish a direct link between the nosocomial infection and the fatal issue of the patients in ICU it has been estimated that in France between 10 000 and 20 000 deaths would be due to this cause.

Several studies documented the risk factors and consequences of nosocomial infection of patients in ICU. However, most of the studies did not take into account the fact that there may be other possible risks, competing with the event concerned – nosocomial infection – ((Ahmed HADDADI, 2013), (Gray RJ, 1988), (Andersen PK, 1985).

Indeed, once the patient has been admitted in ICU, his health can evolve towards one of these three outcomes: being infected with a nosocomial infection, a positive evolution leading to going home or to another healthcare service, a negative evolution, that is, death. His survival would depend on a competition of risks, one outcome preventing the other two outcomes from happening.

The nosocomial infection has got two competing events: discharge or death competing with each other. Unlike logistic regression, the multi-states models are a very appropriate approach to take into account the competing events (Keiding N, 2001), (Klein JP, 2001).

Indeed, they allow the modelling of the time-dependency of certain procedures (for instance intubation, tracheotomy, respiratory assistance etc...).

Considering these three events (nosocomial infection, discharge or death) thanks to the analysis of two competing models (1 and 2) the aim of this paper is to identify the nosocomial infection risk factors on the one hand, and the causes of death on the other hand.

Methodology

This study is mono-centric and retrospective. The place of the study is Timone University Hospital's ICU, this hospital is known to be one the biggest of this area of France (south-eastern part of the country). Equipped with 1069 beds (793 for adults and 276 for children), it is Europe's third largest hospital. The ICU counts 9 beds.

The admission process – in the ICU- is the following one: the patient is recorded by the emergency unit, the patient is picked up by the Mobile Emergency Unit, the patient is transferred from an other care unit, the patient is transferred from another hospital.

The ethics committees agreed that no approval was needed, as the study was retrospective.

All information related to the identity of the patients will stay confidential.

The ICU-acquired infection diagnostics was based on bacteriological proofs.

The first day of infection is the day of the first positive collection knowing that only the first nosocomial episode was taken into account.

Using a standard form we systematically collected the following datas: age, gender, dates of ICU admission, end of the stay, the number of days spent at the ICU before the onset of the first nosocomial infection, the total number of days spent in hospital, the clinical settings (comorbidities, reason of hospitalization), origins of the patient, type of pathology, type of infection and pathogenic causal agents.

We reported all the invasive procedures (intubation, tracheotomy, urinary catheter, central catheter, sedation), the duration of antibiotics before and after the nosocomial incident.

The following scores were estimated for every included patient: the LOD (Logistic Organ Dysfunction) score, he SAPS II (Simplified Acute Physiology Score**)** and the SOFA (Sequential Organ Failure Assessment).

Analysis of the nosocomial infection risk factors (Model 1)

After his admission (state 0), the patient evolves towards the two following states: Infected (state 1) or discharged (state 2) (dead or alive) (Figure 1).

The impact of the two groups of risk factors was documented as far as the two competing models were concerned: the baseline risk factors (origin, male, antibiotic therapy at the admission, cancer, diabetes, transplant, hemopathy, infection at admission, chronic kidney disease, type of patient), and the time-dependent risk factors (death, intubation, antibiotic therapy, CVC (central venous catheter), arterial catheter, sedation, tracheotomy, urinary catheter, discharge).

It should be noticed that apart from the age and the gravity scores values (LOD, SAPSII, SOFA), all risk factors were introduced in the model quoted before as binary variables.

Analysis of the death risk factor (Model 2)

In this model the evolution of the patient's state proceeds with the following pattern: after his admission (state 0) the evolution is either unfavourable and the patient dies (state 1) or favourable and the patient is discharged (state 2) (figure 1).

The impact of the same risk factors (baseline and time-dependent) as in Model 1 was documented. However, we will notice that the acquisition of a nosocomial infection was analysed on the basis of the time-dependent factor.

Using the SAS software (v9.2.) two distinct Cox models were implemented. An analysis of the competing models was done for each model thanks to the cause-specific hazards (Andersen P, 1993), (Tai BC, 2001).

The first step consisted in calculating the cause-specific hazard ratio

for each risk factor with no preselecting. The global significance of the two models was tested using a multivariate analysis at level p= 5%.

The second step consisted in improving the two models by taking out, step by step, the less significant variables as follows: we first selected the factors with a P-value of greater than 0.2 for the two events.

We then evaluated the average of the P-values of these factors and took out the factor that obtained the highest average of P-values. We thus took out all the possible factors. We reiterated this process in applying a threshold of 0.1.

This left us with a model where all the variables became significant, with a value P-values ≤5 % for at least one event.

The selection of the model (Improved versus non improved) was based on the Akaike information criterion (A.I.C.): that is, the lower the AIC value, the better the model. Thanks to the correlation matrices of each Cox model, we could verify if there was any correlation between the different risk factors. The test of significance used is the chi-square.

The cumulative incidence was determined for the most significant risk factors of each model.

The cumulative incidence functions are adapted to illustrate an intuitive representation of the risk of occurrence of an event confronted by a competing event.

They enable us to evaluate the probability for a healthy subject at time “s” to become ill at time “u” evaluated between “s” and “t”, knowing that between “t” and “u”, such a subject may be in one state or the other.

On the other hand they enable us to check the probability for a healthy subject at time “s” to die between “s” and “u” without becoming ill.

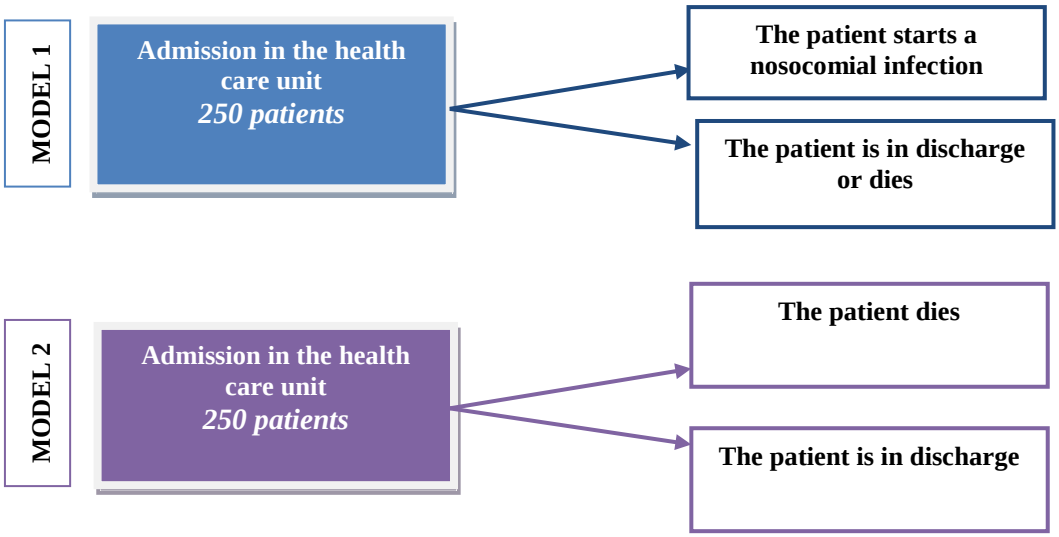

Figure 1: competing models

Results

Out of a total of 565 patients hospitalized from January 1st 2011 to June 30th 2012; we focused our study on 291 patients aged ≥ 18 with a ≥ 3 days stay.

Among these eligible patients, 41 were excluded because of missing data. 46 (18.40%) of the 250 selected patients developed at least one nosocomial episode.

The results corresponding to the gravity scores, the number and the baseline risk factors and time-dependent risk factors are described in Tables 1, 2 and 3.

However, we point out that 62.51% of the isolated bacteria were Gram-positive vs 37.49% of Gram-negative bacteria and that a resistant profile was mentioned among 23.91% of the bacteria.

Scores	Mean	SD (Standard Deviation)
LOD	5.95	2.99
SAPSII	46.51	15.99
SOFA	5.78	2.51
Age	60.23	14.49

Table 7: Statistics describing the baseline type continuous variables

Variable	Number	Percentage
Origin	76	30.4
Antibiotics during admission	22	8.8
Cancer	30	12.0
Diabetic	44	17.6
Transplant	7	2.8
Hemopathy	6	2.4
Infection at the admission	41	16.4
Chronic renal failure	8	3.2
Surgery patient	32	12.8
Male gender	158	63.2

Table 8: Frequencies and percentages of binary variables "baseline type" for the 250 patients

Variable	Nombre	Pourcentage
Death	58	23.2
Intubation	199	79.6
Antibiotic therapy	184	73.6
AC	229	91.6
CVC	186	74.4
Sedation	199	79.6
UC	239	95.6
discharge	185	74.0
Tracheotomy	34	13.6

*(**CVC**: Central Venous Catheter, **AC**: Arterial Catheter, **UC**: Urinary Catheter)*

Table 9: Frequencies and percentages of time-dependent type variables for the 250 patients

Risk factors for nosocomial infection Model 1

All the results of the Cause-specific hazard (calculated in multivariable analysis) of the baseline risk factors and of the time dependent risk factors are reported in Table 4.

We notice that out of 21documented risk factors, only 6 are significant at the p =5% level.

The AIC (Akaike information criterion) of the multivariate model with all the risk factors is of 329 for the nosocomial infections and of 969 for the patients in discharge (dead or live).

	Nosocomial Infection			Discharge (dead or alive)		
Risk Factor	**Cause-specific hazard ratio**	**CI 95%**	**P-value**	**Cause-specific hazard ratio**	**CI 95%**	**P-value**
Age	0.98	[0.96 - 1.01]	0.14	0.99	[0.98 -1.00]	0.18
Antibiotherapy	27700000	.	.	0.45	[0.31- 0.66]	<0.01
Antibiotics at the admission	0.95	[0.27 -3.40]	0.94	0.61	[0.35 - 1.06]	0.08
Cancer	0.64	[0.19 - 2.19]	0.48	1.12	[0.73 - 1.72]	0.61
Arterial Catheter	0.72	[0.05 - 9.55]	0.80	1.19	[0.63 - 2.26]	0.59
CVC	8.00	[0.31-206.09]	0.21	0.42	[0.26 -0.68]	<0.01
Diabetics	0.54	[0.21 -1.40]	0.20	1.14	[0.75 -1.73]	0.53
Transplant	0.24	[0.02 -2.30]	0.21	1.70	[0.61 -4.77]	0.31
Hemopathy	6.02	[0.90 -40.09]	0.06	0.58	[0.17 -1.94]	0.38
Infection at the admission	0.16	[0.04 -0.73]	0.02	0.94	[0.63 -1.41]	0.78
Chronic renal failure	54.68	[4.01-746.45]	<0.01	0.35	[0.14 to 0.88]	0.03
Intubation	10.65	[0.48 - 237.59]	0.14	0.72	[0.37 -1.39]	0.32
LOD	0.95	[0.82 - 1.11]	0.52	1.00	[0.93 -1.07]	0.91
Origin	1.22	[0.56- 2.64]	0.62	1.15	[0.80 -1.65]	0.45
SAPS	0.99	[0.96 -1.02]	0.59	1.00	[0.99 -1.01]	0.91
SOFA	1.08	[0.98 -1.19]	0.14	1.05	[0.98 -1.12]	0.16
Male gender	1.81	[0.88 -3.70]	0.11	1.05	[0.76 -1.46]	0.77
Urinary catheter	2060000	.	.	0.30	[0.14- 0.65]	<0.01
Sedation	0.55	[0.09 -3.38]	0.52	0.87	[0.44 -1.71]	0.69
Tracheotomy	2.04	[0.92 -4.52]	0.08	0.26	[0.15-0.46]	<0.01
Surgery patient	0.47	[0.16-1.37]	0.17	1.03	[0.64-1.65]	0.90

Table 10: Nosocomial infection vs discharge: underlining the risk factors (multivariable analysis)

The improvement of Model 1 was done according to the process described in our methodology. It left only 6 variables significant at level p =5% for at least one of the two states.

These are: antibiotic therapy, central venous catheter, and infection at time of admission, urinary catheter, chronic renal failure and tracheotomy.

All the results and pieces of information related to the CSHRs baseline risk factors and those of the time-dependent risk factors are reported in Table 6.

Risk Factor	Nosocomial Infection			Discharge (dead or alive)		
	cause-specific hazard ratio	IC 95%	P-value	cause-specific hazard ratio	IC 95%	P-value
Antibiotic therapy	11700000	.	0.99	0.48	[0.34 - 0.67]	<0.01
CVC	9.08	[1.10 - 75.20]	0.04	0.40	[0.28 - 0.57]	<0.01
Infection at admission	0.15	[0.04 - 0.64]	<0.01	1.05	[0.72 - 1.51]	0.81
Chronic renal failure	8.99	[1.92 - 42.12]	<0.01	0.36	[0.15 - 0.85]	0.02
Urinary catheter	1620000	.	1.00	0.26	[0.13 - 0.53]	<0.01
Tracheotomy	2.69	[1.45 - 5.01]	<0.01	0.28	[0.17 - 0.47]	<0.01

Table 6: Nosocomial infection vs discharge or death: identification of the significant risk factors at α=5% (Improved model)

The AIC results of the present model – Improved model – are lower than those of the initial model- The AIC value is 314 for the nosocomial infection and 952 for the patients in discharge (dead or alive). On the other hand, the correlation matrices do not show any relationship between the different factors.

The cumulative impact functions are adapted to illustrate the results of an analysis of competing risk factors.

In the case of the present model (Improved Model 1), the cumulative incidence functions of the three most significant risk factors were established (Figure2). These are tracheotomy, CVC and chronic renal failure. Unlike the patients with no tracheotomy, the cumulative incidence function of nosocomial infection among tracheotomised patients is higher, very early, and quickly. It stabilizes after 20 days.

As far as the event is concerned (death or alive), the cumulative incidence function among patients with a tracheotomy is much lower than it is for the patients with no tracheotomy.

Furthermore, out of the patients affected with chronic renal failure, the cumulative incidence function for (death or discharge) is much lower than it is for patients who are not affected with that condition.

Concerning the cumulative incidence function, the patients affected with chronic renal failure show an increase per stage, which seems to stabilize after 5.8 days.

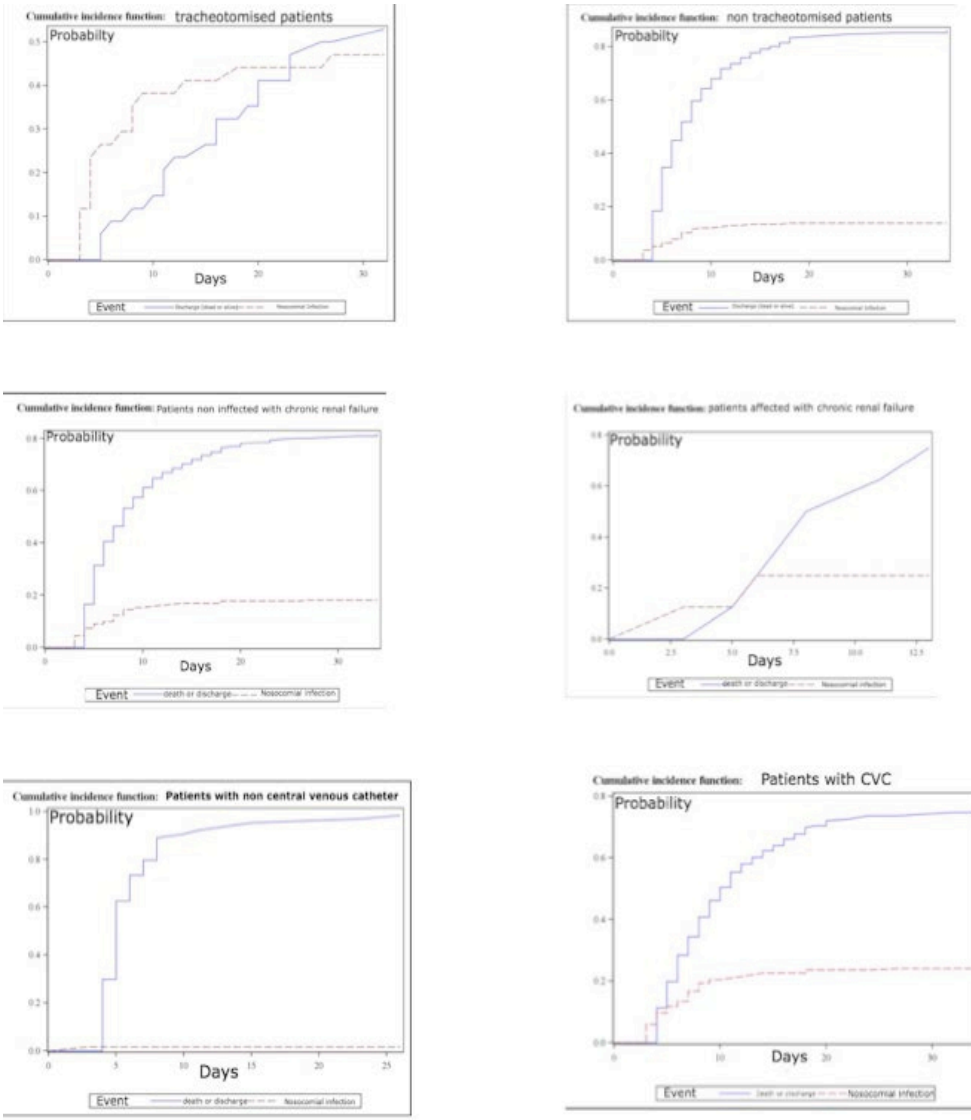

Figure 2: Cumulative incidence functions of (death or discharge) and nosocomial infection among tracheotomised patients versus non tracheotomised patients, among patients affected with chronic renal failure versus patients with no chronic renal failure and (CVC patients vs non CVC ones)

Multivariate analysis of death risk factors for Model 2 – Table 10

It is pointed out that only 11 risk factors are significant at level p =5% for at least one of the events. The values of the AIC for model 2 reporting all the risk factors are the following: 411 for the dead patients and 975 for the patients in discharge.

Risk Factor	Death			Discharge		
	Cause-specific hazard ratio	CI 95%	P-value	Cause-specific hazard ratio	CI 95%	P-value
Age	1.01	[0.98 -1.03]	0.68	0.99	[0.98 -1.00]	0.14
Antibiotherapy	0.44	[0.21 - 0.92]	0.03	0.75	[0.47 - 1.21]	0.24
Antibiotics at the admission	1.11	[0.41- 3.02]	0.84	0.52	[0.30 - 0.91]	0.02
Cancer	3.11	[1.58 to 6.13]	<0.01	0.74	[0.42 - 1.31]	0.30
Arterial Catheter	0.26	[0.07 - 0.89]	0.03	1.50	[0.72 -3.12]	0.28
CVC	0.56	[0.21 - 1.49]	0.25	0.45	[0.26 - 0.78]	<0.01
Diabetics	1.80	[0.90 - 3.60]	0.09	0.95	[0.60 - 1.50]	0.82
Transplant	6.20	[1.18 - 32.50]	0.03	0.79	[0.23 - 2.74]	0.71
Hemopathy	1.59	[0.20- 12.38]	0.66	0.72	[0.21- 2.48]	0.60
Infection at the admission	0.75	[0.34 - 1.65]	0.48	0.76	[0.48- 1.20]	0.24
Chronic renal failure	0.43	[0.10 - 1.91]	0.27	0.35	[0.12 -1.02]	0.05
Intubation	0.43	[0.11 - 1.70]	0.23	1.01	[0.50 - 2.05]	0.98
LOD	0.88	[0.77 - 1.01]	0.08	1.09	[1.01 -1.17]	0.02
Origin	1.85	[0.94 - 3.65]	0.07	1.37	[0.94 - 2.00]	0.10
SAPS	1.02	[1.00 - 1.05]	0.10	0.99	[0.97 -1.00]	0.05
SOFA	1.43	[1.27 - 1.61]	<0.01	0.89	[0.81- 0.98]	0.01
Male gender	1.19	[0.65 - 2.18]	0.57	0.97	[0.69 - 1.36]	0.87
Urinary catheter	7.16	[0.29 - 174.53]	0.23	0.27	[0.12 - 0.64]	<0.01
Sedation	1.50	[0.37 - 6.05]	0.57	0.63	[0.30 - 1.30]	0.21
Tracheotomy	0.03	[0.01 - 0.16]	<0.01	0.34	[0.20 -0.57]	<0.01
Surgery patient	0.91	[0.36 - 2.28]	0.84	1.00	[0.62 - 1.62]	0.99
Nosocomial Infection	0.31	[0.13 - 0.73]	<0.01	0.43	[0.26 - 0.70]	<0.01

Table 10: Death versus discharge: highlighting the risk factors in a multivariable analysis

The selection of variables of the second model operated in accordance with the statistic methodology described before leads to a model consisting in 10 significant variables at level p=5%: antibiotic therapy, CVC, cancer, transplant, LOD score, SAPS II score, SOFA score, urinary catheter, tracheotomy and nosocomial infection.

All the results and information related to the CSHRs of the baseline risk factors and of time-dependent risk factors, significant at level p =5% for

at least one of the two states in the improved model obtained in a multivariable analysis are reported in Table 12.

	Death			Discharge		
Risk Factor	**Cause-specific hazard ratio**	**IC 95%**	**P-value**	**Cause-specific hazard ratio**	**IC 95%**	**P-value**
Antibiotic therapy	0.49	0.26 to 0.92	0.03	0.72	0.48 to 1.09	0.12
Cancer	2.69	1.48 to 4.89	<0.01	0.79	0.45 to 1.38	0.40
CVC	0.38	0.18 to 0.84	0.02	0.52	0.34 to 0.78	<0.01
Transplant	7.30	1.83 to 29.19	<0.01	0.55	0.17 to 1.77	0.32
LOD	0.89	0.77 to 1.01	0.08	1.08	1.00 to 1.16	0.04
SAPS	1.02	1.00 to 1.04	0.10	0.98	0.97 to 1.00	0.01
SOFA	1.36	1.23 to 1.51	<0.01	0.87	0.80 to 0.95	<0.01
Urinary catheter	1.99	0.24 to 16.50	0.52	0.26	0.12 to 0.57	<0.01
Tracheotomy	0.06	0.02 to 0.24	<0.01	0.36	0.22 to 0.57	<0.01
Nosocomial Infection	0.31	0.13 to 0.70	<0.01	0.51	0.33 to 0.80	<0.01

Table 12: Death vs discharge: highlighting of the significant risk factors at level α=5% for at least one of the two states obtained in a multivariable analysis.

We noticed that the AIC of the improved Model 2 are lower than those of the initial Model 2: The AIC of the multivariable model counting only significant risk factors at level α =5% for at least one of the two states are 407 for dead patients and 976 for patients in discharge.

Moreover, the correlation matrices do not show any link between the factors, the improved model is thus of better quality. The cumulative incidence function -Figure 3, are about this three significant risk factors: tracheotomy, CVC and nosocomial infection.

The charts show that among the patients with no tracheotomy, the CIF of the discharge event becomes higher, very early and quickly, and is much more significant than the death event. We also notice that the CIF of tracheotomised patients' death is less significant than that of the group of patients who did not have a tracheotomy.

As far as the patients with a CVC are concerned, they have a death CIF that is much more significant than the group of patients who don't have one.

For the discharge event, the comparison is less obvious than in the CVC group.

As for the patients with a nosocomial infection, the CIF of the event « discharge » is less significant than the CIF of the non-infected patients.

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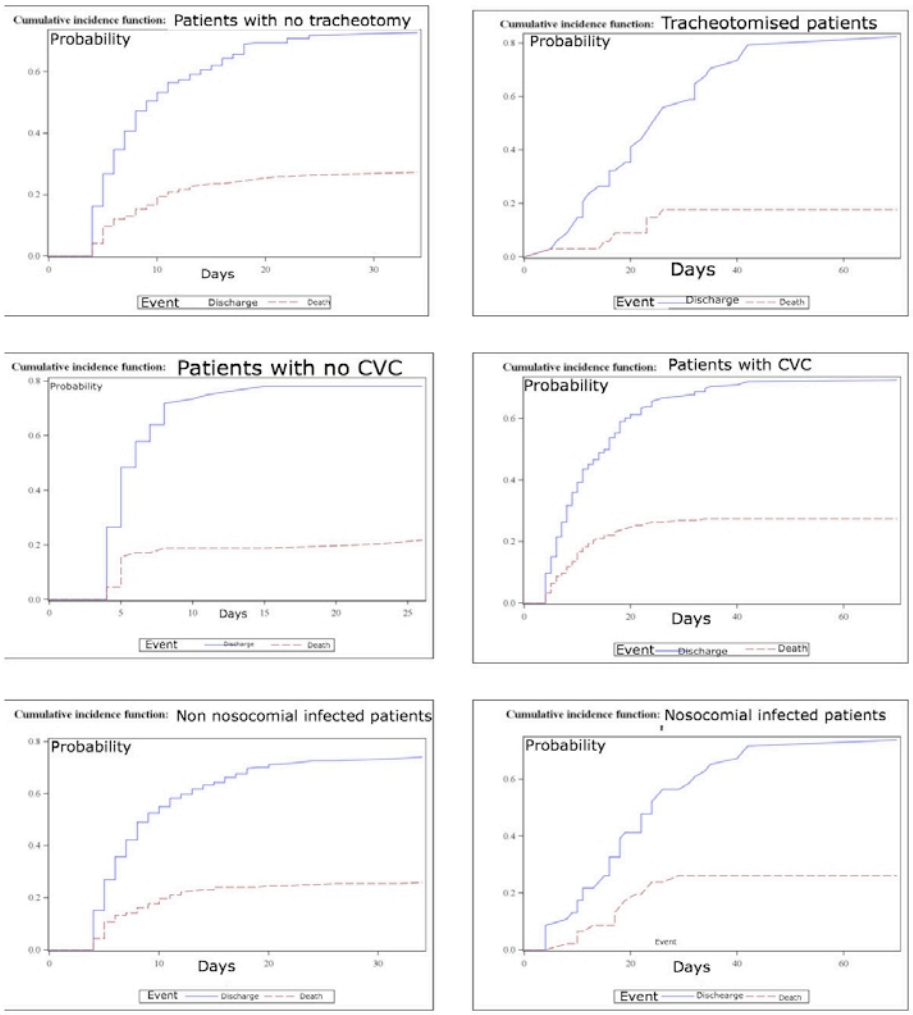

Figure 3: CIF (Cumulative incidence function) of death and discharge of (tracheotomised patients vs non tracheotomised ones), of (CVC patients vs non CVC ones) and of (nosocomial patients vs non infected ones).

Discussion

Several studies documented the nosocomial infection risk factors and the death risk factors in ICU.

Among these factors, we point out: age, gender, a former stay in ICU, the length of stay, a pejorative Glasgow score (GCS), a high (APACHE) II score, a high SAPS II, respiratory failure, congestive heart failure, acute renal failure, dialysis, bronchoscopy, tracheotomy, re-intubation, the length of mechanical respiration, multidrug-resistant pathogen, CVC, bacteremia, enteral nutrition and corticosteroids, (Therneau T, 2000), (Apostolopoulou E, 2003), (Sofianou DC, 2000), (Georges H, 2000), (Ibrahim EH, 2001), (Rello J, 2002), (Pawar M, 2003), (Erbay RH, 2004), (Boots RJ, 2005), (Myny D, 2005), (Tejerina E, 2006), (Gastmeier P, 2007).

However, in most of these studies the effect of time-dependent factors was not taken into account. Schoenfeld and al, pointed out that it was more important to study the death event than the day of death. They suggest that mortality should be analyzed as a binary variable (30 days mortality) using logistic regression (Schoenfeld D, 2006). Thus these risk factors are often modeled with binary forms (present or absent). However, this binary consideration (present or absent) would be a bias according to (Van Walraven C, 2004).

Also notice that in most of these papers, the competing events – nosocomial risk death event or discharge – are not taken into account or modeled in any other way.

However, according to Hyun J Lim, and al, as soon as the patient acquires an event other than the one considered, the probability of knowing this event is *de facto* modified (Hyun J Lim, 2010).

We also point out that Resche-Rigon and al, report that the event «discharge of the patients » should be taken into account as a competing risk to that of death in ICU (Resche-Rigon M, 2006).

In the present studies, we considered two multi-state models in order to precisely study the two important factors, that is the time-dependence risk factors and the competing risks.

With the competing risk models, Kaplan-Meier's estimate (Kaplan EL, 1958), (cumulative hazard function, {1 - SKM(t)}), which does account neither the informative censure -as for instance death while the patient is achieving remission (Kaplan EL, 1958), (Gaynor JJ, 2006), (Pepe MS, 1993), seems to be inappropriate for the calculation of the cumulative incidence.

This lack would be due to the fact that this method overestimates the probability of occurrence of the event of interest (Gaynor JJ, 2006), (Pepe MS, 1993), (Lin DY, 1997), (Southern DA, 2006), (Kalbfleisch JD, 2002).

The bias is even more important when the risk of competing events is high (Putter H, 2007).

Thus, the methodology of analysis applied in our study is an alternative to the one of the cumulative hazard function. Indeed, the Cox cause-specific hazard (Cox DR, 1972) and the cumulative incidence function (CIF) are appropriate approaches to analyze competing risks (Kalbfleisch JD, 2002).

The Cause-specific hazard indicates the instantaneous rate of occurrence of a given event among the patients with no infection (Kalbfleisch JD, 2002), (Kalbfleisch JD, 1978).

The CIF indicates the proportion of patients contracting an event at a definite time t- corresponding to the event.

In Model 1, antibiotic therapy presents a high-risk report in favor of the appearance of a nosocomial event. However, it is not significant at all (p-value = 0.99). This could be explained by the fact that all the patients with a nosocomial infection were under antibiotic therapy. Thus the model cannot be estimated (all the data being separated).

Moreover, we notice that with antibiotic therapy the period of time before the event – death or discharge – is longer (CSHR=0.48).

We can draw the same conclusion as far as the « urinary catheter » factor is concerned (CSHR=0.26). However, we should moderate the fact that the presence of a urinary catheter may lengthen the period of time when the event « death » or « discharge » is due to take place. Indeed, almost 96% of the patients in study had been given a urinary catheter.

The infections at admission show a « protective » role against infection (CSHR=0.15). Indeed, this could be explained by the administration of antibiotics to infected patients when they are admitted in the service. The Martin Wolkewitz study dealing with the risk of nosocomial pneumonia agrees with our analysis. It gives a CSHR = 0.02 for pneumonia at the admission (Martin Wolkewitz, 2008).

In ICU, tracheotomy, whose therapeutic aim is often to provide a respiratory alternative, generates with its process a significant risk (partially or entirely) for nosocomial infection. Indeed, mechanical respiration, which is an integral part of the process, is related in the study (Martin Wolkewitz, 2008) as the main risk factor for the development of nosocomial pneumonia, with an increase of the CSHR of 5,90.

In the present studies, even if this is not as clear as in the improved model, tracheotomized patients seem to be the most vulnerable ones when confronted by nosocomial risk (CSHR=2.69).

We also notice that this slows down the event « death or discharge » significantly (CSHR=0,28). This can also be seen in Figure 2.

In Model 2, antibiotic therapy is reported as being a factor in postponing death (CSHR=0.49). On the other hand, one cannot draw any conclusion with regards to the event « discharge ».

As for the urinary catheter, its presence leads inevitably to a longer stay and affects the « discharge » event (CSHR=0.26). This analysis is confirmed in study (Martin Wolkewitz, 2008). In addition, even if no conclusion can be drawn as far as its implication in the event « death » is concerned, it would be logical to think that patients with a urinary catheter have more risk to get a nosocomial infection. The natural process being an entry, it is followed by colonization and infection.

On the other hand the Central venous catheter seems to have a severe impact on death risk (CSHR=0.38) and also on a smaller scale on the event « discharge » (CSHR=0.42). It significantly extends the length of stay. This strengthens its role of nosocomial infection provider, reported in model 1 (CSHR=9.08) p-value =0.04.

As far as tracheotomy is concerned, it appears to be an important factor in postponing death (CSHR=0.06). The same conclusions were reported by Combes A and al (Combes A, 2007).

The curves for the event « death » in the group of tracheotomized patients clearly show this tendency.

We can also conclude that on the same model for the CVC factor, tracheotomy postpones death but lengthens the stay.

On the other hand, with a (CSHR=2.69), the patients with cancer seem to be more at risk to die. However, we should keep in mind that a combination of variables must be referred to (confounding factors) when we calculate the cancer factor (Staudinger T, 2000).

As far as the gravity scores are concerned, though the LOD and SAPS II scores are significant – for the discharge event – an increase of one score unit « SAPS II » does not mean that there will be an impact on the « discharge » event (CSHR=0.98).

On the contrary the SOFA score results show that an increase of one unit would increases the risk of death (CSHR=1.36) and affects at the same time the event « discharge » (CSHR=0.87).

The results of the studies - done with several different methods of analysis – giving data on the impact on the nosocomial event- give rise to a great many conflicting views.

Thus, contrary to the results by Magnason S and al, (Magnason S, 2008) and Gastmeier P and al, (Gastmeier P, 2005) which claim that the nosocomial event strongly increases the risk of death, those of the present paper reveal that a nosocomial infection can postpone the death event (CSHR=0.31) but lengthen the stay in hospital (CSHR=0.51).

These results can also be observed on the diagram entitled « cumulative incidence function » (Figure 3).

We also notice that after more than 10 days spent in the health care unit, a patient with no nosocomial infection has a 50% chance of survival. On the other hand, a patient contracting a nosocomial infection has less than 15 % chances of survival.

Several limits in the present studies should be mentioned such as the size of the study population, the fact that the study was monocentric and done retrospectively

Conclusion

Nosocomial infection and mortality in ICU have multiple and complex risk factors. It would be a methodological mistake to reduce their analysis to the presence or the absence of infection.

In the present study, the methodology of analysis seems to be the most adequate, for it considers every transitory step - or most of them- of the patient's state.

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