A MULTI-STATE MODEL FOR THE ANALYSIS OF FUNCTIONAL DECLINE AND MORTALITY OF FRAIL ELDERLY PATIENTS

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ABSTRACT

The aim of this study, corresponding to a research project on functional decline and mortality of frail elderly patients, is to build a predictive survival process which takes into account the functional and nutritional evolution of the patients over time. We deal with both survival data and repeated measures but the usual statistical methods for the joint analysis of longitudinal and survival data are not appropriate in this case. As an alternative we use the multi-state survival model approach to evaluate the association between mortality and the recovery, or not, of normal functional and nutritional levels. Once the model is estimated and the prognostic factors of mortality identified, a predictive process is computed which allows predictions to be made of a patient's survival based on their history at a given time. This provides a more exact estimate of the prognosis for each group of patients which may be very helpful to clinicians in the making of decisions.

RESUM

L'objectiu d'aquest estudi, que correspon a un projecte de recerca sobre la pèrdua funcional i la mortalitat de persones grans fràgils, és construir un procés de supervivència predictiu que tingui en compte l'evolució funcional i nutricional dels pacients al llarg del temps. En aquest estudi ens enfrontem a l'anàlisi de dades de supervivència i mesures repetides però els mètodes estadístics habituals per al tractament conjunt d'aquest tipus de dades no són apropiats en aquest cas. Com a alternativa utilitzem els models de supervivència multi-estats per avaluar l'associació entre mortalitat i recuperació, o no, dels nivells funcionals i nutricionals considerats normals. Després d'estimar el model i d'identificar els factors pronòstics de mortalitat és possible obtenir un procés predictiu que permet fer prediccions de la supervivència dels pacients en funció de la seva història concreta fins a un determinat moment. Això permet realitzar un pronòstic més precís de cada grup de pacients, la qual cosa pot ser molt útil per als professionals sanitaris a l'hora de prendre decisions clíniques.

RESUMEN

El objetivo de este estudio, correspondiente a un proyecto de investigación sobre la pérdida funcional y la mortalidad de ancianos frágiles, es construir un proceso de supervivencia predictivo que tenga en cuenta la evolución funcional y nutricional de los pacientes a lo largo del tiempo. En este estudio nos enfrentamos al análisis de datos de supervivencia y medidas repetidas pero los métodos estadísticos habituales para el tratamiento conjunto de este tipo de datos no son apropiados en este caso. Como

alternativa utilizamos los modelos de supervivencia multi-estados para evaluar la asociación entre mortalidad y recuperación, o no, de los niveles funcionales y nutricionales considerados normales. Después de estimar el modelo y de identificar los factores pronósticos de mortalidad es posible obtener un proceso predictivo que permite hacer predicciones de la supervivencia de los pacientes en función de su historia concreta hasta un determinado momento. Esto permite realizar un pronóstico más preciso de cada grupo de pacientes, lo cual puede ser muy útil para los profesionales sanitarios en la toma de decisiones clínicas.

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1 Introduction

In any medical speciality the regular measurement of health and quality of life indicators is known to be an effective tool which allows the perception of the function and patients' capacities to be incorporated into clinical decisions. This is particularly relevant in geriatrics, where evaluations of impairment and disability play a fundamental clinical role.

The goal of this work, which corresponds to a research project on the functional decline and mortality of frail elderly patients, is to build a predictive process which includes the functional and nutritional evolution of the patients over time as prognostic factors of mortality. The data set includes survival times and repeated observations (the functional and nutritional levels of the patients at each visit) and their analysis requires a specific statistical methodology. The problem is that most available methods for the joint analysis of longitudinal and survival data, such as those used by Faucett and Thomas (1996), Wulfsohn and Tsiatis (1997), or Henderson, Diggle and Dobson (2000), are not appropriate for our data. The reasons are, firstly, that these methods do not allow for the use of multivariate markers and, secondly, that due to the mortality of the patients, for many of them we have fewer than three measurements, insufficient for the proper use of the mixed model.

As an alternative we propose to focus our analysis on two clinically relevant aspects of the health progression: whether the normal levels of functional and nutritional status are recovered or not, and the speed of recovery of these normal levels. We use a multi-state survival model to evaluate the association of these two aspects with mortality. Once the model is estimated and the prognostic factors of mortality identified, we can obtain a predictive process of a patient's survival based on their history at a given time. These predictive probabilities are computed as described in Klein, Keiding and Copelan (1994) and Klein and Moeschberger (1998, p. 289-294).

The paper is organized as follows: In Section 2 we describe the cohort study and the follow-up process. In Section 3 we propose specific multi-state models for the analysis of our data set. The resulting predictive process is developed in Section 3.1. A concluding discussion appears in Section 4.

2 Cohort description and follow-up

For many elderly patients an acute medical illness requiring hospitalization is followed by a progressive decline, resulting in high rates of mortality in this population during the year following discharge. However, few prognostic indices have focused on predicting post-hospital mortality in older patients. In order to know more about this question, we analyze a cohort of frail elderly patients older than 75, who have had an acute disease and that, after being treated in an acute care unit, were admitted to the geriatric rehabilitation unit.

A multidimensional geriatric assessment was performed at baseline visit including information on demographics (age, sex, education, living site prior to admission and after discharge ...), cognitive, functional (measured by Barthel index) and nutritional (measured by Mini nutritional assessment) status, presence of depression, co-morbidity and quality of life level. For any patient, information for all assessments was collected either from the patient him/herself (when cognitive performance was intact) or from a knowledgeable informant.

It is a well known clinical fact that, in this kind of cohorts the status of patients at admission is not enough for an accurate prognosis to be made. Instead, the evolution of their functional and nutritional status, especially in the first weeks after admission, might be very informative of the future mortality of these patients. For this reason, , we plan a one year prospective longitudinal follow-up. The patients were visited on admission to the geriatric unit and at around 1, 3, and 6 months after admission. Of course, not all patients were able to attend all 4 visits because of mortality during the follow-up. In addition to this, information on mortality up to 12 months after admission was obtained through telephone interviews.

The cohort included 165 patients with an average age of 83.3 years old (standard deviation of 5.1 years) and 31.5% were male. The average length of stay in the acute care unit was 15.2 days (SD 8.1) and 32% had a good or very good perception of his quality of life before the acute episode of illness. At 6 months accumulated mortality was 29.1% (CI 0.95: 22.2-36.7) and the mortality accumulated at 12 months was 36.4 (IC 0.95: 29.0-44.2).

The functional status of the patients was measured with the so-called Barthel index which consists of a questionnaire dealing with daily activities (bowels and bladder continence, grooming, toilet use, feeding, transfers, mobility, dressing and stairs). In addition of information collected at baseline, 1, 3 and 6 month, for this index the investigators estimated retrospectively the patient functional status 15 days before admission to acute care unit (called preadmission assessment). Barthel index rules between 0 and 100 and a Barthel index lower than 50 indicates the patient is functionally dependent, while a Barthel index higher than 50 is considered to be normal for this kind of cohort. Figure 1 represents the mean profile of the functional status of this cohort. Most of the patients enter the rehabilitation unit with very low Barthel indexes but after a certain time some of them improve, with functional capacity reaching normal Barthel levels.

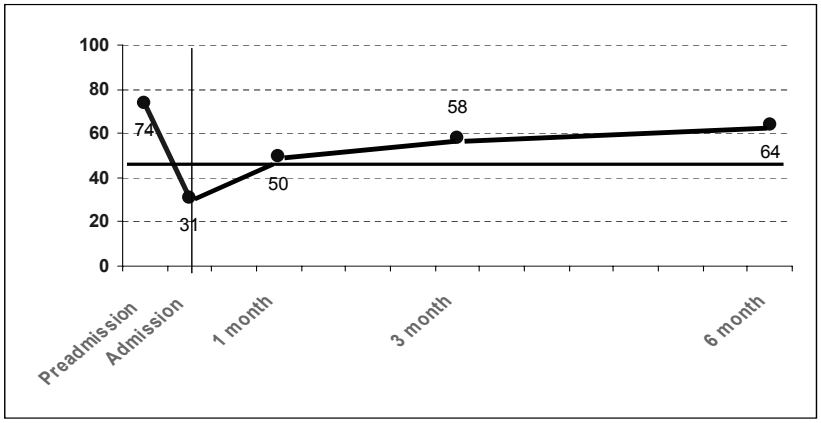

Figure 1: Mean profile of functional status

The nutritional status of patients was measured at each visit with the mini nutritional assessment (MNA) test. This assessment tool can be used to identify patients at risk of malnutrition. It is composed of 18 questions grouped in 4 categories: Anthropometric assessment (weight, height and weight loss), general assessment (lifestyle, medication and mobility), dietary assessment (food and fluid intake and autonomy of feeding), and subjective assessment (self perception of health and nutrition). A total score lower than 20 indicates a risk of malnutrition while a score higher than 20 can be considered as a normal nutritional level for this cohort. In Figure 2 we present the mean profile for the nutritional status of this cohort. As before, most patients enter the unit at risk of malnutrition but after a certain time the nutritional status of some patients improves.

3 Multi-state survival model

As explained in the introduction, the available methods for jointly analyzing longitudinal and survival data using mixed–effect models are not appropriate in this study. As an alternative approach we focus our analysis on two important aspects of the patients' evolution. These two aspects are whether the normal levels of functional and nutritional status are recovered or not and the speed at which this recovery occurs. We use a multi-state survival model approach to evaluate the association of these two aspects with mortality.

We consider two intermediate events defined as follows. We use E_1 to denote the event of a patient's recovery of normal functional levels and, in a similar way, E_2 denotes the event of

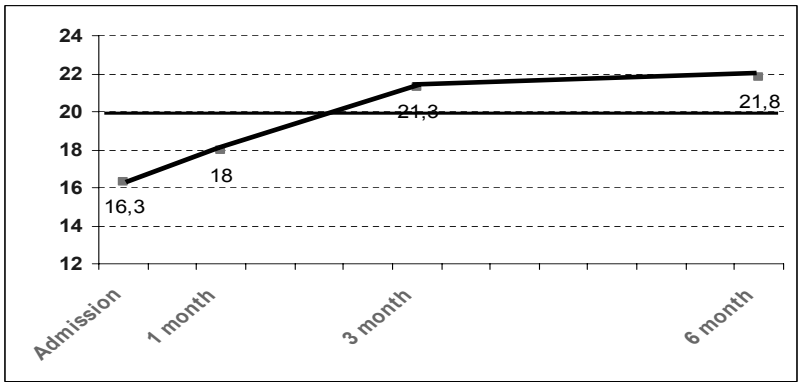

Figure 2: Mean profile of nutritional status

a patient's recovery of normal nutritional levels. All possible paths for a patient who enters the rehabilitation unit are described in the multi-state model represented in Figure 3. There are three survival times involved in this model: the survival time of interest, denoted by T, which is the elapsed time from admission to death, the elapsed time from admission to the occurrence of event E_1 which is denoted by T_B and the elapsed time from admission to the occurrence of event E_2 which is denoted by T_N.

We use Z to denote all fixed covariates measured at admission and define two time-dependent covariates as $B(t) = \mathbf{1}\{T_B \leq t\}$ and $N(t) = \mathbf{1}\{T_N \leq t\}$ which are indicators of whether the normal functional and nutritional levels have been achieved at time t.

The multi-state model in Figure 3 can be analyzed under the proportional hazards assumption with three Cox models (Cox, 1972): a Cox model for the survival time T with $B(t)$ and $N(t)$ as time-dependent covariates

$$\lambda_T(t|Z, B(t), N(t)) = \lambda_{T0}(t) \exp\{\beta_T Z + \gamma_T B(t) + \theta_T N(t)\};$$

a Cox model for T_B, the time to normal functional levels, with $N(t)$ as time-dependent covariate

$$\lambda_B(t|Z, N(t)) = \lambda_{B0}(t) \exp\{\beta_B Z + \theta_B N(t)\}$$

and a Cox model for T_N given $B(t)$ as time-dependent covariate

$$\lambda_N(t|Z, B(t)) = \lambda_{N0}(t) \exp\{\beta_N Z + \gamma_N B(t)\}.$$

When fitting the first model the result we obtained indicated that parameter γ in (1) was not significatively different from zero, that is, time T_B to normal functional levels turned out to be not significant. Thus, our initial multi-state model can be simplified as shown in Figure 4.

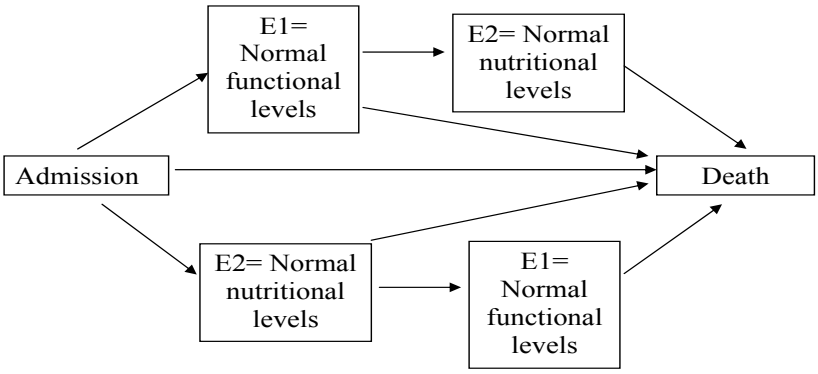

Figure 3: Multi-state model with two intermediate events to describe all possible paths from admission to death

This new multi-state model can be analyzed with only two Cox models: a Cox model for the survival time T with $N(t)$ as time-dependent covariate

$$\lambda_T(t|Z, N(t)) = \lambda_{T0}(t) \exp\{\beta_T Z + \theta_T N(t)\} \tag{1}$$

and a Cox model for T_N

$$\lambda_N(t|Z) = \lambda_{N0}(t) \exp\{\beta_N Z\}. \tag{2}$$

The three hazard functions defined in the new multi-state model (Figure 4) are obtained from models (1) and (2) as follows:

$$\lambda_1(t) = \lambda_T(t|Z, N(t)=1) = \lambda_{T0}(t) \exp\{\beta_T Z + \theta_T\} \tag{3}$$

$$\lambda_2(t) = \lambda_T(t|Z, N(t)=0) = \lambda_{T0}(t) \exp\{\beta_T Z\} \tag{4}$$

$$\lambda_3(t) = \lambda_N(t|Z) = \lambda_{N0}(t) \exp\{\beta_N Z\}. \tag{5}$$

The best fit for the model (1) shows that there are three fixed covariates associated with mortality: gender, nutritional status at admission and functional status before the onset of the acute disease. The results are presented in Table 1. They show that at the moment of admission the risk of mortality of a man is approximately three times that for a woman and that patients with low nutritional levels at admission and with low functional levels before the onset of the acute disease have a higher risk of mortality. This fit also shows that the time taken to regain normal nutritional levels is associated with mortality.

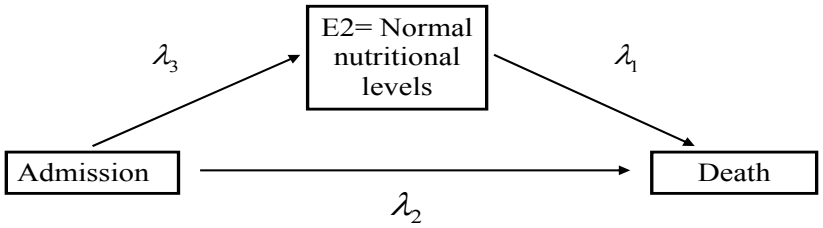

Figure 4: Multi-state model with one intermediate event to describe all possible paths from admission to death

Table 1: Risk coefficient estimates for model 1

		coef	exp(coef)	exp(-coef)	p
gender	$\beta_{1T} = -1.1083$		0.330	3.03	0.000029
barthel (pre-admission)	$\beta_{2T} = -0.0142$		0.986	1.01	0.003800
mna (admission)	$\beta_{3T} = -0.0741$		0.929	1.08	0.027000
N(t)	$\theta_T = -0.9963$		0.369	2.71	0.015000

3.1 Predictive process

The results in table 1 are useful in describing the effect of the fixed covariates on survival but, if our interest is rather in how the process of recovering normal nutritional levels influences the prognosis for a patient, it is more useful to compute what is called the predictive process. The predictive process is defined as the probability of death before time u given that the patient is alive at time t and given the history of this patient at time t:

$$\pi(u,t) = P[t < T \leq u | H(t)]. \tag{6}$$

In our study we have two possible histories:

$$H_1(t) = \{T > t,\ T_N \leq t\} = \{T > t,\ N(t) = 1\}$$

and

$$H_2(t) = \{T > t,\ T_N > t\}\{T > t,\ N(t) = 0\}.$$

The first one, H_1, corresponds to a patient who recovered normal nutritional levels before time t and the second one, H_2, to a patient whose nutritional levels continued to be lower than normal at time t.

The predictive process can be obtained in a closed form for both possible histories, H_1 and H_2, and will be denoted by $\pi_1(u,t)$ and $\pi_2(u,t)$, respectively.
The probability $\pi_1(u,t)$ of death before time u for a patient who at time t is alive and has recovered normal nutritional levels can be obtained by integrating the conditional density over all possible death times between t and u:

$$\begin{aligned}\pi_1(u,t) &= P[t<T\leq u|H_1(t)] = P[t<T\leq u|T>t, N(t)=1] = \\ &= \int_t^u \frac{f_1(s)}{S_1(t)}\,ds = \int_t^u \frac{S_1(s)\lambda_1(s)}{S_1(t)}\,ds = \\ &= \int_t^u \exp\{-(H_1(s)-H_1(t))\}\lambda_1(s)\,ds.\end{aligned}$$

This expression can be estimated with the estimated risk factors obtained from fitting model (1) and using expression (3):

$$\pi_1(u,t) \approx \sum_{t<t_i\leq u} \exp\left\{-\exp\left(\hat\beta_T Z+\hat\theta_T\right)\left(\hat\Lambda_{T0}(t_i)-\hat\Lambda_{T0}(t)\right)\right\}\exp\left(\hat\beta_T Z+\hat\theta_T\right)\hat\lambda_{T0}(t_i)$$

where $\hat\Lambda_{T0}(t)$ is Breslow's estimate of the cumulative baseline hazard function corresponding to model (1).
The probability $\pi_2(u,t)$ of death before time u for a patient who at time t is alive and has not yet recovered normal nutritional levels can be obtained by considering two possibilities: that the patient dies at time s or that the patient recovers normal nutritional levels at time s and then dies between s and u:

$$\begin{aligned}\pi_2(u,t) &= P[t<T\leq u|H_2(t)] = \int_t^u \left(\frac{f_2(s)}{S_2(t)}+\frac{f_3(s)}{S_3(t)}\pi_1(u,s)\right)ds = \\ &= \int_t^u (\exp\{-(H_2(s)-H_2(t))\}\lambda_2(s) + \\ &\quad + \exp\{-(H_3(s)-H_3(t))\}\lambda_3(s)\pi_1(u,s))\,ds.\end{aligned}$$

To approximate this expression we use the estimated risk factors obtained from fitting models (1) and (2) and using the relationship between λ_2 and λ_T when $N(t)=0$ given in expression (4) and the relationship between λ_3 and λ_N given in expression (5):

$$\begin{aligned}\pi_2(u,t) \approx &\sum_{t<t_i\leq u}\left(\exp\left\{-\exp\left(\hat\beta_T Z\right)\left(\hat\Lambda_{T0}(t_i)-\hat\Lambda_{T0}(t)\right)\right\}\exp\left(\hat\beta_T Z\right)\hat\lambda_{T0}(t_i)\right. \\ &\left.\exp\left\{-\exp\left(\hat\beta_N Z\right)\left(\hat\Lambda_{N0}(t_i)-\hat\Lambda_{N0}(t)\right)\right\}\exp\left(\hat\beta_N Z\right)\hat\lambda_{N0}(t_i)\pi_1(u,t_i)\right)\end{aligned}$$

where $\hat{\Lambda}_{T0}(t)$ and $\hat{\Lambda}_{N0}(t)$ are Breslow's estimates of the cumulative baseline hazard function of T and T_N corresponding to model (1) and (2), respectively.
The predictive process depends on the time t at which the history is known and the point s at which we wish to make a prediction. By fixing or varying adequately the values of t and s we can obtain different insights into the problem. In Figure 5 we show the predictive process when fixing $t = 2$ and varying s. This corresponds to the predicted residual survival times for patients 2 months after admission. It is clear that gender is an important risk factor with women having a higher predicted survival time than men. Also, recovering or not normal nutritional levels during the first 2 months appears to be a risk factor, though not a very strong one, that is, the survival curves for women in both categories are very similar as are the survival curves for men in both categories.

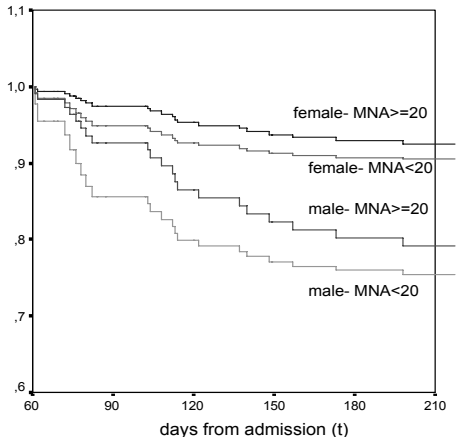

Figure 5: Predicted residual survival curves for patients 2 months after admission

Now we computed the predictive process with $t = 4$ and varying s. This gives the residual survival curves 4 months after being admitted (Figure 6). Here we note that the differences between patients who recovered and those who did not, have increased. In particular, though gender is still an important risk factor, now women who did not recover MNA during the first 4 months after admission have a similar predicted survival time to men who did recover. What these two pictures show is that the recovery, or not, of normal nutritional levels is a dynamic prognostic factor and its impact on mortality varies over time.
This can be seen more clearly in Figure 7. In this graph we have plotted the predictive process with a variable value of t and taking $s = 6 + t$. This corresponds with the probability of death during the next 6 months as a function of the time t from admission. As shown in the Figure, it is clear that the differences between recovering or not recovering normal nutritional levels start to become apparent around 2 months after admission. During these first 2 months the

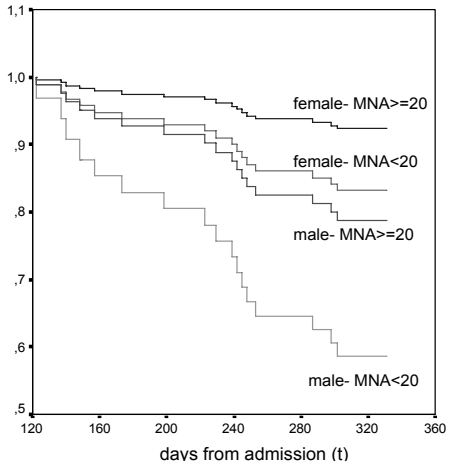

Figure 6: Predicted residual survival curves for patients 4 months after admission

predicted mortality is similar for both categories, while, failure to recover nutritional levels after these 2 months is associated with a higher risk of mortality in the next 6 months for both men and women.

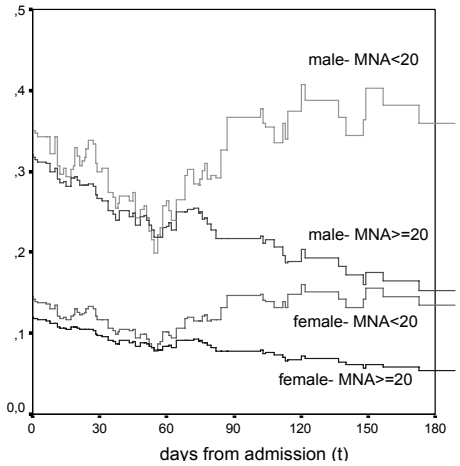

Figure 7: Probability of death during the next 6 months as a function of the time t from admission

4 Discussion

Many medical studies could be improved by introducing information on the evolution of patients and it is worth working on methodologies which deal with this problem.

In this work, on the functional decline and mortality of frail elderly patients, we obtained a predictive process which illustrates the dynamic prognostic power of nutritional evolution of

the patients. Though the data contain both survival and repeated observations, the available methods for the joint analysis of longitudinal and survival data were not appropriate in this case and, as an alternative we propose a multi-state survival model. We obtained that the recovery of normal nutritional levels during the first two months is critical. This methodology gives the clinicians a dynamic tool for prediction.

5 Acknowledgements

The data analyzed correspond to a research project on functional decline and mortality of frail patients. Dr. Espaulella from "Hospital de la Santa Creu de Vic" is the main researcher and the project received financial support in 2002 from the "Acadèmia de ciències mèdiques de Catalunya i de Balears" (a regional academic and scientific association). The authors have provided methodological support to the researchers. We gratefully acknowledge the comments and opinions we have received from the doctors and nurses at the "Hospital de la Santa Creu de Vic", which have helped and encouraged us in the study and implementation of this methodology.

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