A side-effects mapping model in patients with lung, colorectal and breast cancer receiving chemotherapy

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***Abstract*—Cancer treatments are now more effective than ever and, as a consequence, cancer is becoming a chronic disease. Chemotherapy is a frequently used treatment in people with cancer and it can cause a number of side-effects which if not properly managed could have a negative impact on the patients' quality of life. In this study, a sample of 56 patients receiving chemotherapy treatment for breast, colorectal and lung cancer is considered; each experienced side-effect is recorded during four consecutive treatment cycles (each lasting 14 days). Five of the most frequent side-effects (fatigue, nausea, mucositis, hand and foot sore, diarrhoea) are selected to build a comprehensive model which predicts the probability of experiencing a certain symptom on a specified day of each cycle of therapy. The computed accuracy of results shows that the newly proposed model has an enhanced predictive power compared to a state-of-the-art approach. The information gained from this study will help medical and nursing staff caring for such patients to more accurately predict the side-effects that patients will experience and therefore select appropriate help to minimise, whenever possible, the influence of those symptoms.**

I. Introduction

A. Background

It is estimated that in 2007 almost 300,000 individuals in the United Kingdom were diagnosed with cancer and over the last 25 years, cancer incidents have considerably increased [1] [2] [3] [4]. However, different treatments are available depending on the type and stage of cancer and the survival rates have been improving over the last 30 years; in particular, besides surgery an adjuvant chemotherapy treatment is often given: this helps to reduce the risk of cancer recurrence or death from microscopic spread of the cancer that is suspected (but cannot be detected) and also it may alleviate cancer related symptoms with a consequent improvement in patients' quality of life [5] [6]. However, it is to be noted that adjuvant chemotherapy exposes patients to risk of significant side-effects that could have a negative impact on patients' quality of life and daily living [7] and also on the maintenance of dose intensity treatment, which could influence the disease free and overall survival [8] [9]. A poor assessment and management of symptoms in patients with cancer have been ascertained [10]. It has also been observed that poorly informed patients are less likely to comply with treatment and are more likely to experience anxiety and hence a general reduction in their quality of life [11] [12]. As a consequence, an effective prediction of side-effects could help medical staff with better management of patients' needs, with special regard to discomfort minimization, unnecessary worry and anxiety reduction.

B. Clinical decision support systems

Multiple studies [13] [14] [15] have shown that, for different reasons, health care is suboptimal; since there is often a major discrepancy between clinical care actually delivered and optimal patient care, alternative care models in traditional primary care are being actively explored. Published studies of clinical decision support systems (CDSSs) are increasing and their quality is also improving [16] [17]: such systems can enhance clinical performance for drug dosing and prescribing, preventative care, diagnosis, disease management and other aspects of medical care. Different tools have been proposed as clinical decision support system in many clinical fields. With regard to cancer care, studies tend to focus on predictors of survival and life threatening toxicities [18] [19] [20]. In relation to the prediction of symptoms, only a few risk models have been presented [21].

C. Related work

The use of technology to communicate between healthcare professionals and patients may lead to improvements in quality of life and symptom control, reductions in the rate of hospitalizations, emergency department visits and cost savings [22]. Patients also appear to have positive views of using this type of technology, reporting improvements in communication with healthcare providers [23].

The Advanced Symptom Management System (ASyMS©) has been developed and trialled as an example of the use of technology in cancer care [24] [25] [26] [27]. It has been built as a mobile telephone-based remote symptom monitoring system which can be used to register, monitor and predict the side-effects of chemotherapy while the patient is not with a healthcare professional [28]. First, patients using the system are asked to complete a symptom questionnaire on a mobile phone twice a day and sent this information directly to their hospital-based healthcare professional. Self-care advice is then given on the basis of the reported symptoms. Depending on

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their seriousness, an alert is generated to the healthcare professional via a 24 hour dedicated pager system. The healthcare professional is then informed of the symptoms that the patient has reported and may contact the patient if necessary. This system also allows nurses to monitor the symptoms remotely and facilitates the delivery of relevant and useful advice to the patient based on their current symptoms.

Next, the tool uses the patients' symptom history as well as a model developed based on a corpus of patients with similar medical conditions to predict the likely side effects a patient could expect over the course of treatment: patients are able to receive predictions concerning the possible symptoms they are going to experience throughout the course of treatment along with daily predictions that are updated as they enter data describing their own symptoms.

A diary is presented on patients' mobile phones where, for each day, a smiley, sad or neutral face is used to depict the overall side-effects situation predicted for that particular day: patients who wish to plan ahead can see at a glance which days they are more likely to feel well. Users may select any of the symptoms to see self-care advice on how to manage this symptom; they will also be able to see how many more days they are likely to experience each symptom.

D. Aims

The aim of this study is to evaluate, improve and generalize the pilot model proposed by a previous study [29] using an enhanced dataset and according to a common set of performance metrics. In the previous study a number of different simple mathematical equations were developed to predict the probability of experiencing each symptom on a specified day of treatment, for patients with breast cancer. The idea was to build on the previously presented remote monitoring system for patients. The objective of the present research is to generalise the previous model to build a more powerful and comprehensive side-effect risk model for patients with cancer undergoing adjuvant chemotherapy: this model is not limited to breast cancer but has been extended to cover colorectal and lung cancer conditions. A single mathematical model, which predicts on a day-by-day basis the symptoms that patients with cancer receiving chemotherapy are going to experience, has been proposed. The new model can be used as a tool to provide preparatory information to patients with cancer receiving chemotherapy and to their carers. An improvement in the patients' experience is expected by providing information on the side-effects that they are likely to experience on each day of treatment; furthermore, the provision of tailored information and possibly medications based on their individual needs can also be facilitated in the future by such a model.

II. Methods

A. Study sample

The collection of data has been carried out as part of previous research [30], over a 12-month period from June 2007 to May 2008: 56 patients' data from four clinical sites in Scotland were collected, although only patients with breast cancer were considered within the cited study. Selected patients were diagnosed with breast, colorectal and lung cancer, starting a course of adjuvant chemotherapy, aged 18 years or over, able to read and write English and all deemed by members of the clinical team to be physically and psychologically fit to participate in the study. Ethical approval was gained from the study sites, and all patients provided written informed consent before their participation in the study. The observation of each patient involved treatment over four cycles, each lasting 14 days, where treatment was administered at the beginning of each cycle. For each patient the following data are used for this study: number of the cycle (between 1 and 4), number of the day within the cycle (1 to 14), symptoms experienced among the five object of our model. Patients are grouped as follows: patients with breast cancer (N=34), with colorectal cancer (N=9) and with lung cancer (N=13).

B. Pre-modelling

A previous study [29] has shown that the probability of experiencing a specific symptom is basically time dependant. In different ways, each of the five considered symptoms has two main tendencies over time that could be outlined: a 'peak effect', around the day in which the treatment is received by patients, and an 'inverted U-shape effect', rising from a low on the day after treatment to a peak around mid-cycle before falling again. In this study a more general model is proposed which combines these two effects. Moreover, since differences between cycles were outlined, a cycle-dependant coefficient was added in order to capture those differences. Following this setting, a comprehensive model is proposed as per formula (1)

$$P(d) = a \cdot S(d) + b \cdot H(d) + \sum_{n=1}^{4} c_n \cdot D_n \qquad (1)$$

where:

- $P(d)$ is the probability of experiencing a specified symptom on day d;
- D_n is a dummy variable which is set to 1 for the n-th cycle and 0 on other cycles;
- $S(d)$ is a function capturing the 'inverted U-shape effect';
- $H(d)$ is a function capturing the 'peak effect';
- a, b, c_n are coefficients determined for each symptom.

$S(d)$ is built so that $S(first\,day) = S(last\,day) = 0$ and $S(middle\,day) = 1$; in a similar way, $H(d)$ is build so that $H(first\,day) = 1$ and $H(last\,day) = 0$. Lots of functions could be adopted to be used as $S(d)$ and $H(d)$. For the purpose of this study a sinusoid function and a negative hyperbolic function have been chosen by trial and error.

Having 14 days within each cycle (and so $d_{max} = 14$), the adopted formulas for these two terms are reported in equations (2) and (3).

$$S(d) = sin\left(\frac{d-1}{d_{max}-1}\pi\right) = sin\left(\frac{d-1}{13}\pi\right) \qquad (2)$$

$$H(d) = \frac{d_{max}}{d_{max}-1}\left(\frac{1}{d} - \frac{1}{d_{max}}\right) = \frac{14}{13}\left(\frac{1}{d} - \frac{1}{14}\right) \qquad (3)$$

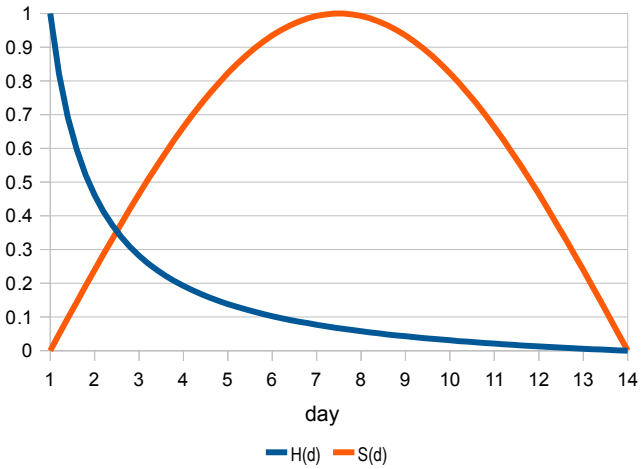

Fig. 1. Chosen functions

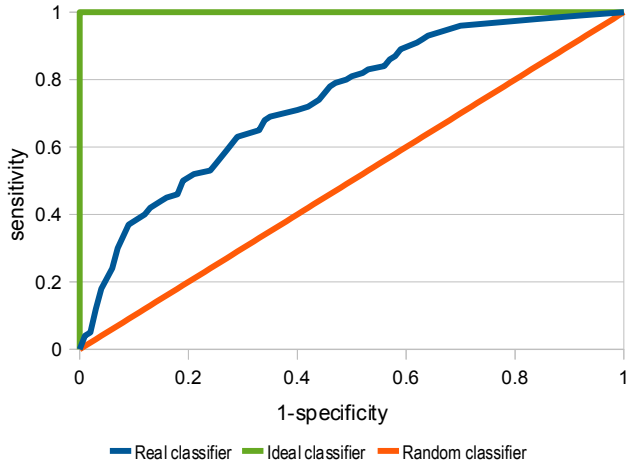

Fig. 2. Examples of ROC curve

The chosen functions are reported in Fig. 1.

C. Data analysis

Raw data collected from different patients about symptoms experienced in the same day of the same cycle have been grouped after dividing the dataset into three subsets for breast, colorectal and lung cancer respectively. If they experienced a certain symptom on that day the considered output was 1, otherwise 0. After grouping the outputs, these were averaged for each group, giving a probability of experiencing that symptom at the corresponding time.

Then, a regression (one each for breast, colorectal and lung cancer) was run in order to estimate the coefficients for the variables outlined above. Some metrics have been computed in an attempt to better explain the predictive power of the model: p-values for each coefficient and R^2 of regression for each symptom. Finally, for each symptom, the receiver operating characteristic (ROC) curve has been used to estimate the goodness of the newly developed model to compare this with the previous model.

D. Performance metrics

The outcome of the model is the probability of experiencing a specified symptom on a specified day and cycle. In order to measure the performance of the model, the probabilities given by the model were converted to a 'yes' or 'no' value, using a cut-off point.

Generally speaking, false positive and false negative could have different kind of implications (clear examples of which are shown in [31] [32] [33]): as a consequence, the decision threshold used to separate positive and negative outcomes has a certain grade of arbitrariness depending on the desired false positive over false negative ratio. Nevertheless, the predictive power of a model should be evaluated regardless of the chosen cut-off point. For this reason, ROC curves have been adopted as they provide an index of accuracy by determining the limits of a test's ability to discriminate between alternative states of health over the complete spectrum of operating conditions [34]. A ROC curve can also be considered a plot of the probability of correctly classifying the positive cases against the rate of incorrectly classifying true negative ones: in other words, for each possible value of the decision threshold, a pair of true-positive and false-positive performance rates are represented on the ROC curve.

On Fig. 2, the diagonal line represents the ROC curve of a random classifier, the angular line shows the performance of an ideal classifier, and the other line corresponds to an example of the ROC curve for the proposed model. The more the ROC curve tends to be near to the upper left corner, the better the performance is: the area under curve (AUC) is used as a performance metric and it usually varies from 0.5 for a random classifier to 1.0 for an ideal classifier (i.e. 100% of true positive and no false negative are detected). However, it has to be pointed out that since patients in the same group (i.e. during the same day of the same cycle) may have experienced different symptoms, the ideal AUC=1.0 cannot be reached.

The AUC has been used to evaluate the performance of the proposed model and to compare it with the previously used model. Moreover, in order to measure the goodness of fit and the significance of regression of the proposed model, the standard coefficient of determination (R^2) and the p-values associated with the coefficients are also computed.

III. Results

A. Area under ROC curve

On Tab. I the AUC for the proposed model and for the previously used model is reported for each symptom. In order to make a fair comparison with the available benchmark (which used only patients with breast cancer), the performance related to breast cancer are also evaluated separately. From the results tabulated on Tab. I and also depicted in Fig. 3, it is clear that the proposed model significantly outperformed the previous model.

B. R^2 and p-values

In a linear regression, the coefficient of determination (or R^2) is the proportion of variability in a data set that is

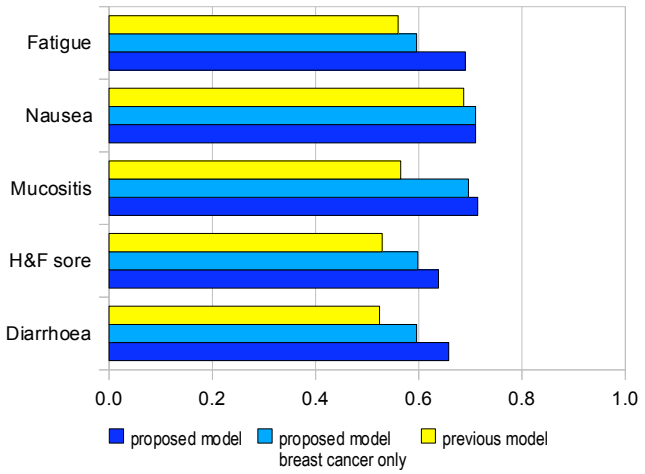

Fig. 3. Comparison of performance for each symptom

TABLE I
AUC FOR CURRENT AND PREVIOUS MODELS

#	Diarrhoea	H&F sore	Mucositis	Nausea	Fatigue
1	0.658	0.638	0.714	0.710	0.690
2	0.596	0.598	0.696	0.710	0.596
3	0.524	0.529	0.565	0.687	0.560

#1: proposed model - breast, colorectal and lung cancer
#2: proposed model - breast cancer only
#3: previous model breast cancer only [29]

TABLE II
COMPARISON OF R^2

	Diarrhoea	H&F sore	Mucositis	Nausea	Fatigue
Breast	0.746	0.837	0.900	0.850	0.960
Colorectal	0.595	0.686	0.742	0.721	0.588
Lung	0.469	0.836	0.910	0.796	0.960

accounted for by the statistical model and it varies between 0 and 1. So, the higher is the R^2, the better is the goodness of fit. Coefficients of determination for each symptom and type of cancer are given in Tab. II (in this case, the R^2 coefficients measures the proportion of the variability in the dependent variable about the origin explained by regression - since the coefficients for identifying the cycle are treated as dummy variables - and so this coefficient cannot be compared to a similar one for models which include an intercept).

Each coefficient derived from the linear regression is associated with a p-value, showing the probability of observing the data if the associated coefficient was equal to zero. So, a high p-value indicates that the variable associated to the coefficient does not improve the global model.

P-values associated with each coefficient are tabulated on Tab. III, Tab. IV and Tab. V.

C. Analysis

Data about cycle and day of treatment seem to have a good (and sometimes excellent, considering that the maximum attainable AUC is less than 1) predictive power for all the listed

TABLE III
P-VALUES FOR BREAST CANCER REGRESSION MODEL

	Diarrhoea	H&F sore	Mucositis	Nausea	Fatigue
S	0.227	0.016	0.001	0.001	0.001
H	0.314	0.101	<0.001	<0.001	0.088
D_1	0.006	0.022	<0.001	0.588	<0.001
D_2	0.001	<0.001	0.012	0.305	<0.001
D_3	0.057	<0.001	<0.001	0.836	<0.001
D_4	<0.001	<0.001	<0.001	0.132	<0.001

TABLE IV
P-VALUES FOR COLORECTAL CANCER REGRESSION MODEL

	Diarrhoea	H&F sore	Mucositis	Nausea	Fatigue
S	0.149	0.051	0.655	0.024	0.938
H	0.125	0.639	0.392	0.035	0.671
D_1	0.012	0.018	0.147	0.001	<0.001
D_2	0.099	<0.001	0.001	<0.001	0.030
D_3	0.009	<0.001	<0.001	<0.001	0.090
D_4	0.934	0.020	0.626	0.054	0.702

TABLE V
P-VALUES FOR LUNG CANCER REGRESSION MODEL

	Diarrhoea	H&F sore	Mucositis	Nausea	Fatigue
S	0.209	0.454	0.075	0.760	0.915
H	0.672	0.423	0.795	0.704	0.038
D_1	0.784	<0.001	<0.001	<0.001	<0.001
D_2	0.024	<0.001	<0.001	<0.001	<0.001
D_3	0.891	<0.001	<0.001	0.001	<0.001
D_4	0.269	0.293	0.016	<0.001	<0.001

symptoms. Also, the overall performance of the model seems to confirm that the effects observed for treatments of breast cancer (inverted U-shape and peak effects) may be re-usable for other kinds of cancer. However, as reflected by the lower R^2 (especially for colorectal cancer) these effects may be able to explain a smaller part of the variability of the proposed model. Moreover, p-values associated with coefficients show that the two main effects, while being statistically significant for many symptoms in patients with breast cancer, could not be generally seen as definitely relevant during the treatment of colorectal or lung cancer (assuming a significance level of 5%), except for both effects in determining nausea for patients with colorectal cancer and for inverted U-shape effect in prediction of fatigue for patients with lung cancer.

Two examples of the model's outcome for some symptoms are reported in Fig. 4 and Fig. 5.

IV. DISCUSSION

The main aim of this study was to improve results produced by previous state-of-the-art models for prediction of side-effect symptoms experienced by patients with breast cancer receiving adjuvant chemotherapy, extending the model also for colorectal and lung cancers. The model combines, for the first time, the two empirically determined effects: specifically the peak effect and the inverted U-shape effect, for which two

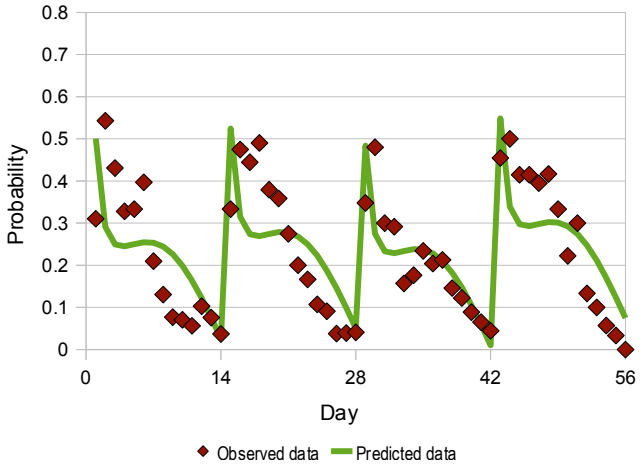

Fig. 4. Representation of probability given by the model (nausea for breast cancer)

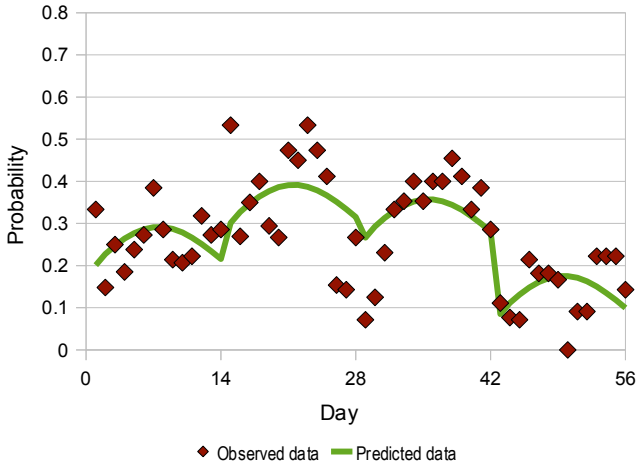

Fig. 5. Representation of probability given by the model (mucositis for lung cancer)

different functions were chosen by trial and error. From the analysis of chosen performance metrics, the model seems to have generally reached the envisaged performance providing an average increase of 19% in comparison with the previous model: this demonstrates the potential of these kinds of models in the management of chemotherapy related toxicities within clinical practice. Some limitations should also be noted: first, the considered sample of patients was not so large and was not equally distributed between breast, colorectal and lung cancer; a second limitation relates to the fact that the available data covered just four cycles of chemotherapy, while most adjuvant breast cancer chemotherapy regimens consist of six to eight cycles; finally, data about different administered treatments are not available at present. These three limitations are sufficient to prevent this model from being directly used in clinical practice; however, the new model offers fertile ground for further research and development. A range of contributions and potential impact is envisaged from this work both for clinical practice and further research. On clinical practice, patients could know in advance which symptom they should expect and when, and health professionals could take appropriate action wherever possible in order to avoid or, at least, minimize expected discomforts. From the point of view of future research in this interdisciplinary area, a comprehensive model has been proposed for time series symptom analysis: which is expandable with different non-linear basis functions and the general outlined framework has also shown how to select possible variables which require to be considered or excluded to improve the model giving, as a by-product, some new insights on symptoms' pattern within each cycle, between different cycles and between different treatments. This added-value aspect can also be further researched and new insights correlated with clinical findings.

V. Conclusion

This work successfully built on a previous state-of-the-art tool for side-effect modelling on patients with cancer undergoing adjuvant chemotherapy treatment. The proposed model has been both generally improved and may be reusable in different contexts. Whilst the encouraging results reported in this small-scale study should be taken with care, they do illustrate the potential of this kind of a time series modelling approach. For future work, further large-scale investigations using larger datasets will be carried out and different modelling techniques will be applied (using different types of basis functions) with a view to providing a reliable model that could be potentially deployed in clinical practice.

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