RESEARCH ARTICLE

Clinical Prognostic Score for Predicting Disease Remission with Differentiated Thyroid Cancers

Charoonsak Somboonporn[1]*, Ampica Mangklabruks[2,3], Ammarin Thakkinstian[4], Patravoot Vatanasapt[5,6], Suwannee Nakaphun[7]

Abstract

Background: Differentiated thyroid cancer is the most common endocrine malignancy with a generally good prognosis. Knowing long-term outcomes of each patient helps management planning. The study was conducted to develop and validate a clinical prognostic score for predicting disease remission in patients with differentiated thyroid cancer based on patient, tumor and treatment factors. Materials and Methods: A retrospective cohort study of 1,217 differentiated thyroid cancer patients from two tertiary-care hospitals in the Northeast of Thailand was performed. Associations between potential clinical prognostic factors and remission were tested by Cox proportional-hazards analysis in 852 patients (development cohort). The prediction score was created by summation of score points weighted from regression coefficients of independent prognostic factors. Risks of disease remission were estimated and the derived score was then validated in the remaining 365 patients (validation cohort). Results: During the median follow-up time of 58 months, 648 (76.1%) patients in the development cohort had disease remission. Five independent prognostic factors were identified with corresponding score points: duration from thyroid surgery to ^{131}I treatment (0.721), distant metastasis at initial diagnosis (0.801), postoperative serum thyroglobulin level (0.535), anti-thyroglobulin antibodies positivity (0.546), and adequacy of serum TSH suppression (0.293). The total risk score for each patient was calculated and three categories of remission probability were proposed: ≤1.628 points (low risk, 83% remission), 1.629-1.816 points (intermediate risk, 87% remission), and ≥1.817 points (high risk, 93% remission). The concordance (C-index) was 0.761 (95% CI 0.754-0.767). Conclusions: The clinical prognostic scoring model developed to quantify the probability of disease remission can serve as a useful tool in personalized decision making regarding treatment in differentiated thyroid cancer patients.

Keywords: Differentiated thyroid carcinoma - radioiodine - remission - factors

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Introduction

Differentiated thyroid cancer (DTC) is the most common endocrine malignancy with generally good prognosis. The 10-year survival rates for papillary and follicular thyroid cancer were 93-94% and 84-85% respectively (Hundahl et al., 1998; Mazzaferri and Kloos, 2001). In Thailand, it is among the top ten leading cancers in females, with an age standardized incidence rate of 3.6 in females and 1.1 in males per 100,000 population (Sriplung et al., 2005). The incidence has been increasing during the recent years as reported from many countries (La Vecchia et al., 2015). Total thyroidectomy followed by radioactive iodine (^{131}I) treatment together with life-long thyroid hormone is a treatment strategy for most patients (Haugen et al., 2016). Knowing outcomes of each patient helps initial and long-term management plan of individual patient. Several prognostic factors for DTC patients have been studied mainly focusing on mortality and disease recurrence (Yildrim, 2005; Welsch et al., 2007), but less for disease remission. In addition, more attention has been paid to individualized treatments. This emphasizes the need to build an accurate and practical prognostic rule for predicting the disease progression of patients. This study was therefore conducted, which aimed to develop and internally validate a prognostic model for predicting disease remission in patients with DTC.

Materials and Methods

Patients

A retrospective cohort study was conducted by

*[1]Department of Radiology, [5]Department of Otorhinolaryngology, [6]Cancer Unit, Faculty of Medicine, Khon Kaen University, Khon Kaen, [2]Department of Internal Medicine, Faculty of Medicine, [3]The Research Institute for Health Sciences, Chiang Mai University, Chiang Mai, [4]Section for Clinical Epidemiology and Biostatistics, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, [7]Nuclear Medicine Division, Maharat Nakhon Ratchasima Hospital, Maharat Nakhon Ratchasima, Thailand *For correspondence: charoonsak.som@gmail.com*

identifying patients from thyroid cancer databases, the Nuclear Medicine Division, Srinagarind Hospital (SNGH), Khon Kaen University; and Maharat Nakhon Ratchasima Hospital (MHNH). Both hospitals are tertiary-care, referral hospitals in the Northeast of Thailand. A total of 1,217 patients were referred to these hospitals for post-thyroidectomy ^{131}I treatment during 1995-2007 and 1997-2007, respectively. The study protocol was approved by the local ethics committee of both hospitals. The inclusion criteria were patients with histology-confirmed DTC (papillary carcinoma or follicular carcinoma) who underwent thyroid surgery and postoperative ^{131}I treatment. The exclusion criteria were patients with contraindication for ^{131}I treatment or refused ^{131}I treatment.

Treatment protocols of these two hospitals were similar, mainly based on international treatment guidelines, such as those of American Thyroid Association published in 1996 (Singer et al., 1996) and 2006 (Cooper et al., 2006), and of Asia Pacific Panel published in 2006 (Sundram et al., 2006). Briefly, post-therapy whole body scan was performed a week after ^{131}I treatment to determine the extent of disease. A few days after ^{131}I treatment, thyroxin was initiated and continued to suppress serum thyroid-stimulating hormone (TSH) level. The patients were then followed up at a 6-month interval until remission, and every 6-12 month after remission. Patients who did not come to the clinic were contacted by phone or mail to ask for disease status.

Outcome and prognostic factors

Our primary outcome was disease remission, which was defined if patients were met all the following three criteria: no clinical evidence of tumor, negative pathologic uptake on ^{131}I diagnostic whole body scan, and stimulated serum thyroglobulin (Tg) <10 ng/mL together with negative serum anti-thyroglobulin antibodies (anti-TgAb) (Mazzaferri, 2005). The time to disease remission was defined as the time since the date of initial thyroid surgery to the remission date. Those patients who were lost to follow-up, or had persistent disease at the end of the study were treated as censored at date of last follow-up and end of study date (31 December 2009).

Three domains with 13 potential prognostic factors were considered including domain of patient, tumor and treatment (Loyo et al., 2013; Fatima et al., 2014; Thamnirat et al., 2015). Patient domain consisted of gender, age at diagnosis, duration of symptoms before diagnosis, duration from initial thyroid surgery to the first ^{131}I treatment, and postoperative stimulated serum Tg together with serum anti-TgAb positivity at the time of the first ^{131}I treatment. Tumor pathologic domain included histology, size of primary tumor, the presence of extrathyroid extension, cervical lymph node metastasis, and distant metastasis at initial diagnosis. Treatment-related factors included completeness of thyroid surgery and adequacy of thyroid hormone suppressive therapy. Total thyroidectomy and near-total thyroidectomy were considered as complete surgery, whereas less than near-total thyroidectomy was considered incomplete surgery. Upon the follow-up before remission, the patient was considered to have adequate TSH suppression if more than 80% of TSH measurements were ≥0.5 mIU/L.

Statistical analyses

All variables were abstracted from medical records. Data for six prognostic factors were missing with a range of 6.4% - 38.8%, including duration of symptoms before diagnosis, tumor size, serum Tg level, anti-TgAb positivity, evidence of extrathyroid extension, and evidence of cervical lymph node metastasis. A simulation-based sequential multivariate regression analysis with chain equations was applied to impute missing data (Rubin and Schenker, 1991; White et al., 2011). Complete data (e.g. age, gender, histology, etc) as well as the outcomes of interest were used to predict the missing values with 20 imputations (van Buuren et al., 1999).

Seventy percent (852 patients) of the entire complete cohort was random for development of prognostic score, whereas the remaining 30% (365 patients) was used for score validation.

To make simplify prognostic score, some continuous factors were dichotomized based on previous studies (Raef et al., 2008; Edge and Compton, 2010) and clinical reasoning as follows: age at diagnosis <45 versus ≥ 45 years, duration of symptoms ≤12 versus > 12 months, size of primary tumor ≤4 versus > 4 cm, duration from thyroid surgery to ^{131}I treatment ≤3 versus > 3 months, postoperative serum Tg level ≤9 versus > 9 ng/mL, and suppressible serum TSH ≤80% versus >80% of all measurements. A simple Cox proportional hazard regression model was performed by considering each individual factor and disease remission. Candidate factors whose p-value <0.2 in this step were then considered in a multivariate Cox model. A likelihood ratio with forward selection was applied to select parsimonious model. A prognostic score for individual factor was then created using its regression coefficient obtained from the parsimonious model. A total score was then calculated by summing up scores for all independent prognostic factors. The score cut-off values were next calibrated using receiver operating characteristic (ROC) curve analysis. The cut-offs were selected according to the estimated positive likelihood ratio (LR+) derived from each cut-off.

The score performance was evaluated for discrimination ability. Discrimination refers to the ability to distinguish between patients with and without remission, and is quantified using the concordance C-index which is a generalization of the area under the ROC curve. The C-index of 0.5 has no discrimination power at all, whereas 1.0 indicates perfect discrimination (Pencina and D'Agostino, 2004). For internal validation, estimation of remission probability was done using the derived scoring model on each patient in the validation cohort. Calibration for the probability of remission between the prediction by using scoring model and actual observation was performed. A perfect calibration would show identical predicted probabilities and the observed probabilities.

A p-value less than 0.05 was considered to be statistically significant unless otherwise specified. All data analyses were performed using STATA software, version 10.0.

Results

The entire cohort included 1,217 patients: 973 (80%) from SNGH and 244 (20%) from MHNH. The median follow-up time was 58 months. All patients underwent primary thyroid surgery. Of these, 1,095 (90%) patients had complete thyroid surgery. Initial lymph node surgery was performed in 244 patients (20%). Additional subsequent therapy included chemotherapy, external beam radiation, and surgery in 3, 12, and 24 patients, respectively. Outcome data were available for all patients. Of the entire cohort, 914 cases (75.1%) developed disease remission but 6 patients died before disease remission. Baseline characteristics of the patients in the score development and the score validation sets before data imputation were similar as presented in Table 1.

Score development

Of 852 patients in development data, 648 had disease remission with the time at risk of 37,020 person-month. The median time to remission was 21.1 months, and the incidence rate was 0.024.

Univariate analysis of candidate prognostic variables for disease remission is demonstrated in Table 2. All variables showed significant association with the outcome at p-value <0.2, except tumor histology and extrathyroid extension. The final model identified in multivariate analysis showed that duration from thyroid surgery to ^{131}I treatment ≤3 months (HR 2.06, 95% CI 1.69-2.50), absence of distant metastasis at initial diagnosis (HR 2.23, 95% CI 1.58-3.13), postoperative serum Tg ≤9 ng/mL (HR 1.71, 95% CI 1.39-2.08), positive anti-TgAb (HR 1.73, 95% CI 1.12-2.69), and adequate TSH suppression during follow-up (HR 1.34, 95% CI 1.13-1.59) were associated with a higher probability of disease remission (Table 3).

Based on the regression coefficients, the prognostic score for remission was calculated by the formula: the total score of each patient = 0.721 A + 0.801 B + 0.546 C + 0.535 D + 0.293 E. A represented the duration from thyroid surgery to ^{131}I treatment (0 for > 3 months and 1 for ≤3 months); B represented distant metastasis at initial diagnosis (0 for present and 1 for absent); C represented serum anti-TgAb positivity (0 for negative and 1 for positive); D represented serum Tg level (0 for

Table 1. Characteristics of Patients in the Model Development and Validation Group

Characteristics	Development set (Total 852)	Validation set (Total 365)
Gender		
Female	728 (85.5%)	299 (81.9%)
Male	124 (14.6%)	66 (18.1%)
Age at diagnosis (years)*	42.2 (±14.0)	43.1 (±12.9)
Duration of symptoms (months)*	42.0 (±60.0)	42.9 (±55.8)
Histology		
Papillary carcinoma	683 (80.2%)	285 (78.1%)
Follicular carcinoma	169 (19.8%)	80 (21.9%)
Size of primary tumor (cm)*	2.4 (±1.8)	2.5 (±2.1)
Extrathyroid extension		
Absent	415 (81.9%)	153 (75.4%)
Present	92 (18.2%)	50 (24.6%)
Cervical node metastasis		
Absent	270 (51.2%)	111 (50.9%)
Present	257 (48.8%)	107 (49.1%)
Distant metastasis		
Absent	766 (89.9%)	328 (89.9%)
Present		
Lung	40 (4.7%)	14 (3.8%)
Bone	19 (2.2%)	8 (2.2%)
Lung and bone	6 (0.7%)	6 (1.6%)
Others	21 (2.5%)	9 (2.5%)
Type of initial thyroid surgery		
Total thyroidectomy	702 (82.4%)	286 (78.4%)
Near-total thyroidectomy	67 (7.9%)	40 (11.0%)
Subtotal thyroidectomy	77 (9.0%)	35 (9.6%)
Unilateral lobectomy	6 (0.7%)	4 (1.1%)
Initial lymph node surgery		
Not performed	678 (79.6%)	295 (80.8%)
Performed	174 (20.4%)	70 (19.2%)
Duration from thyroid surgery to radioiodine treatment (months)*	5.4 (±18.4)	5.0 (±18.7)
Postoperative preablation serum Tg (ng/mL)*	117.2 (±398.6)	103.7 (±237.9)
Additional external beam radiation treatment		
Not performed	840 (98.9%)	360 (99.2%)
Performed	9 (1.1%)	3 (0.8%)
Additional chemotherapy		
Not performed	851 (99.9%)	363 (99.5%)
Performed	1 (0.1%)	2 (0.5%)
Additional surgery		
Not performed	832 (97.9%)	359 (98.4%)
Performed	18 (2.1%)	6 (1.6%)
Cumulative dose of 131I (mCi) before remission or end of follow-up*	205.4 (±190.3)	220.6 (±222.3)

The number and percent are of the non-missing values in the original database; *Variables are presented as mean + SD

level > 9 ng/mL or positive anti-TgAb, and 1 for ≤9 ng/mL); E represented adequacy of TSH suppression (0 for ≤80% and 1 for > 80% suppressible measurements). The possible total score ranged from 0 to 2.361. Three categories of probability of remission were estimated for the scoring model according to the following cutoffs: ≤1.628 points (low risk, 83% remission), 1.629-1.816 points (intermediate risk, 87% remission), and ≥1.817 points (high risk, 93% remission). Kaplan-Meier survival curves for probability of remission, according to the three risk score categories are shown in Figure 1.

Score discrimination, calibration, and validation

The score discriminated moderately well between the patients who did and did not develop disease remission with the C-index of 0.761 (95% CI 0.754-0.767) in the development cohort (Figure 2). When the score was applied to the validation group, the C-index was 0.745 (95% CI 0.736-0.755), indicating similar discrimination ability in external data, although this difference was statistically significant (p-value 0.0067). In addition, close agreement between the predicted and observed probabilities with our model was shown across various

Table 2. Univariate Analysis for Disease Remission in the Development Group

Characteristics	HR (95%CI)	P-value
Gender		
Male	1	
Female	1.30 (1.02, 1.66)	0.035
Age at diagnosis (years)		
≥ 45	1	
< 45	1.24 (1.05, 1.46)	0.01
Duration of symptoms (months)		
>12	1	
≤12	1.32 (0.92, 1.91)	0.129
Histology		
Follicular carcinoma	1	
Papillary carcinoma	1.11 (0.91, 1.34)	0.303
Size of primary tumor (cm)		
> 4	1	
≤4	1.32 (0.92, 1.91)	0.129
Extrathyroid extension		
Present	1	
Absent	1.14 (0.88, 1.47)	0.328
Cervical node metastasis		
Present	1	
Absent	1.37 (1.14, 1.65)	0.001
Distant metastasis		
Present	1	
Absent	2.47 (1.76, 3.46)	<0.001
Duration from thyroid surgery to ^{131}I treatment (months)		
> 3	1	
≤ 3	2.01 (1.66, 2.43)	<0.001
Completeness of thyroid surgery		
Incomplete	1	
Complete	1.35 (1.04, 1.77)	0.026
Postoperative preablation serum Tg (ng/mL)		
> 9	1	
≤ 9	1.85 (1.52, 2.24)	<0.001
Positive anti-TgAb	1.80 (1.17, 2.79)	0.008
Acceptable TSH suppression test during follow-up (%)		
≤80	1	
> 80	1.14 (1.19, 1.67)	<0.001

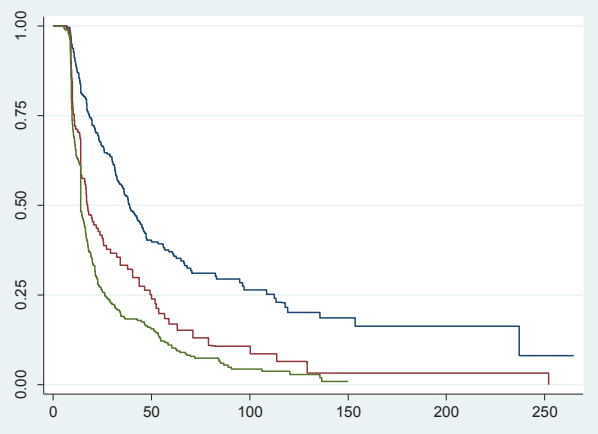

Figure 1. Kaplan-Meier Survival Curves for Probability of Remission, According to the Three Risk Score Categories

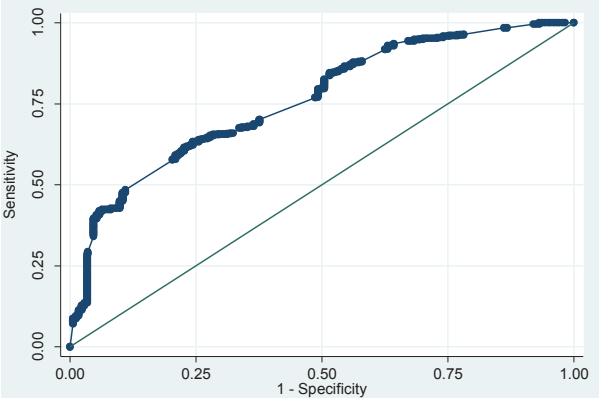

Figure 2. Scoring Model Discrimination Performance

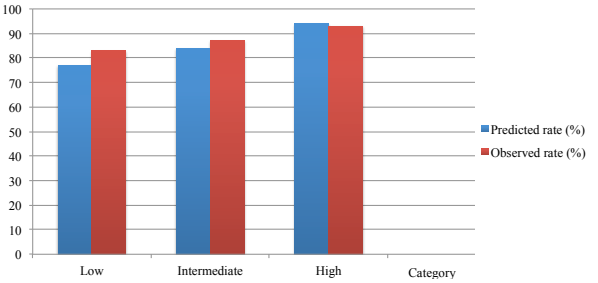

Figure 3. Probabilities of Remission between Using Scoring Model and Actual Observation in the Validation Cohort

Table 3. Multuvariate Analysis for Disease Remission in the Development Group

Characteristics	Regression coefficient	HR (95% CI)	P-value
Duration from thyroid surgery to ^{131}I treatment	0.721	2.06 (1.69, 2.50)	<0.001
Distant metastasis	0.801	2.23 (1.58, 3.13)	<0.001
Postoperative preablation serum Tg (ng/mL)			
≤9	0.535	1.71 (1.39, 2.08)	<0.001
Positive anti-TgAb	0.546	1.73 (1.12, 2.69)	0.016
Adequacy of TSH suppression test during follow-up	0.293	1.34 (1.13, 1.59)	0.001

patient risk categories (Figure 3).

Discussion

We developed a clinical prognostic score for prediction of disease remission in patients with DTC. Five predictors--duration from thyroid surgery to ^{131}I treatment, the presence of distant metastasis in initial diagnosis, serum Tg level and anti-TgAb positivity at the time of first ^{131}I treatment, and adequacy of TSH suppression--with corresponding score points were identified and could be used to estimate the probability of remission of individual patient. A risk stratification indicated that probabilities of disease remission were 83%, 87%, and 93% for low, intermediate, and high scores, respectively. These predictors were readily available in routine clinical practice and easy to use due to their dichotomous nature.

Remission rate in our cohort was about 76%, at the median follow-up time of almost 5 years, which was comparable to those in the range of 75-80% reported earlier (DeGroot et al., 1990; Samaan et al., 1992). Prognostic factors for DTC remission have been studied, though not so extensively as those for recurrence and mortality (Raef et al., 2008; Thamnirat et al., 2015). However, the results were varied, possibly due to different criteria in determining prognostic factors and in defining remission status in each study. Of the five significant prognostic factors, four of them can be defined early in the course of first ^{131}I therapy, including the time period from initial thyroid surgery to ^{131}I treatment, the presence of distant metastasis at initial diagnosis, and serum Tg level, and anti-TgAb positivity at the time of first ^{131}I treatment. Only the adequacy of TSH suppression needs to be documented during the course of follow-up visits before remission.

Although no consensus exists regarding the proper timing of postoperative ^{131}I treatment, if indicated, clinical practice guidelines recommend ^{131}I treatment when serum TSH is higher than 25-30 mIU/L which is about 3-4 weeks after thyroid surgery (Cooper et al., 2009). However, in practice the delay may occur due to no available isolation room for high dose ^{131}I treatment. Our results showed that patients who received ^{131}I treatment within the time period of ≤3 months had a higher probability of remission than those treated > 3 months after thyroidectomy.

The presence of distant metastasis at initial diagnosis, mostly found in the lung or bone, is usually identified by preoperative chest radiograph or ^{131}I post-therapy whole body scan. When present, it would classify patients as stage II or stage IV for the DTC patients <45 and > 45 years of age, respectively (Edge and Compton, 2010). Our findings were in accordance with those reported earlier that the patients with a higher TNM stage or distant metastasis had a higher risk of non-remission (Raef et al., 2008; Garg et al., 2015; Thamnirat et al., 2015). This is also the case for patients with higher serum Tg level at the time of ^{131}I therapy (Fatima et al., 2014; Thamnirat et al., 2015). We found patients with postoperative serum Tg ≤9 ng/mL had a 1.71 chance of having remission higher than those with serum Tg>9 ng/mL.

The presence of serum anti-TgAb may occur in 25% of thyroid cancer patients (Spencer et al., 1999) and renders serum Tg level to become unreliable in indicating disease burden. We intended to classify patients with positive anti-TgAb separately in order to simulate the real clinical practice. Although previous studies have reported serum Tg as a prognostic factor in DTC patients (Fatima et al., 2014; Thamnirat et al., 2015), to our knowledge, our study is the first to address the problem regarding particular patients with unreliable serum Tg due to positive anti-TgAb. We found patients with positive anti-TgAb had a higher probability of having remission compared with those with serum Tg >9 ng/mL. The possible explanation is that positive anti-TgAb can also be found in DTC patients with concomitant lymphocytic thyroiditis. Therefore, elevated serum anti-TgAb may reflect not only disease burden of thyroid cancer but also autoimmune process in these patients (Latrofa et al., 2012).

TSH suppression has been a mainstay in the treatment of DTC. In achieving this, patients with persistent disease need to take regular thyroxin with a daily dose high enough to suppress serum TSH (Cooper et al., 2009). We found that patients with > 80% suppressible TSH measurements had a 1.34 chance of having remission higher than those with suppressible TSH measurements of ≤80%. It is worth noting that this prognostic factor is the only one that is modifiable after initial treatment with surgery and ^{131}I therapy; therefore, patient counseling emphasizing on taking regular thyroxin should be done in order to reach the favorable outcome.

Although previous prognostic model studies for DTC patients are available, their outcomes of interest focused only mortality and disease recurrence (Yildirim, 2005; Welsch et al., 2007). To our knowledge, our study is the first to develop a prognostic scoring model for prediction of disease remission in patients with DTC treated by thyroidectomy and ^{131}I. In addition, our model was built from a cohort comprising a large number of DTC patients. Our prognostic scoring model showed the C-index of 0.761 (95% CI 0.754-0.767), indicating in discriminating patients who would and would not develop disease remission.

However, our study had some limitations. Firstly, since this study was a retrospective cohort study, data of some potential prognostic factors were missing. Although multiple imputation method was used to correct this problem, this statistical method could at least partly result in some biased estimates (Vergouwe et al., 2010). Secondly, the data were acquired from nuclear medicine units of the two hospitals. Although protocols in the management of DTC patients of the two hospitals were in line with the available guidelines, a small variety in the treatment protocol, such as the follow-up schedule after ^{131}I treatment, was inevitable. This might affect the time-to-event outcome. Lastly, our clinical score was not a simplified one. The score points from each prognostic factor were the exact original number of regression coefficients and were not rounded to be the integers. However, we believed that with a minor calculation process to get the total score point of each patient, our scoring model is still easy to use in clinical practice. We recommend that external validation of our model should

be carried out before being used in other hospital settings.

In summary, we developed and internally validated a clinical prognostic score for prediction of disease remission in DTC patients by using a large cohort of patients undergoing thyroidectomy and ^{131}I treatment at two referral hospitals. The score performed moderately well in predicting the probability of remission. This score is helpful to inform individual patient more accurately about the future course of disease and to guide patients and clinicians in joint decisions for management plan.

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