Development and validation of a nomogram risk prediction model for malignancy in dermatomyositis patients: a retrospective study

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Background. Dermatomyositis accompanied with malignancy is a common poor prognostic factor of dermatomyositis. Thus, the early prediction of the risk of malignancy in patients with dermatomyositis can significantly improve the prognosis of patients. However, the identification of antibodies related to malignancy in dermatomyositis patients has not been widely implemented in clinical practice. Herein, we established a predictive nomogram model for the diagnosis of dermatomyositis associated with malignancy. **Methods.** We retrospectively analyzed 240 cases of dermatomyositis patients admitted to Sun Yat-sen Memorial Hospital, Sun Yat-sen University from January 2002 to December 2019. According to the year of admission, the first 70% of the patients were used to establish a training cohort, and the remaining 30% were assigned to the validation cohort. Univariate analysis was performed on all variables, and statistically relevant variables were further included in a multivariate logistic regression analysis to screen for independent predictors. Finally, a nomogram was constructed based on these independent predictors. Bootstrap repeated sampling calculation C-index was used to evaluate the model's calibration, and area under the curve (AUC) was used to evaluate the model discrimination ability. **Results.** Multivariate logistic analysis showed that patients older than 50-year-old, dysphagia, refractory itching, and elevated creatine kinase were independent risk factors for dermatomyositis associated with malignancy, while interstitial lung disease was a protective factor. Based on this, we constructed a nomogram using the above-mentioned five factors. The C-index was 0.780 (95% CI: 0.690-0.870) in the training cohort and 0.756 (95% CI: 0.618-0.893) in the validation cohort, while the AUC value was 0.756 (95% CI: 0.600-0.833). Taken together, our nomogram showed good calibration and was effective in predicting which dermatomyositis patients were at a higher risk of developing malignant tumors.

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17   **Abstract**

18   **Background.** Dermatomyositis accompanied with malignancy is a common poor prognostic factor of

19   dermatomyositis. Thus, the early prediction of the risk of malignancy in patients with dermatomyositis can

20   significantly improve the prognosis of patients. However, the identification of antibodies related to malignancy in

21   dermatomyositis patients has not been widely implemented in clinical practice. Herein, we established a predictive

22   nomogram model for the diagnosis of dermatomyositis associated with malignancy.

23   **Methods.** We retrospectively analyzed 240 cases of dermatomyositis patients admitted to Sun Yat-sen Memorial

24   Hospital, Sun Yat-sen University from January 2002 to December 2019. According to the year of admission, the first

25   70% of the patients were used to establish a training cohort, and the remaining 30% were assigned to the validation

26   cohort. Univariate analysis was performed on all variables, and statistically relevant variables were further included

27   in a multivariate logistic regression analysis to screen for independent predictors. Finally, a nomogram was constructed

28   based on these independent predictors. Bootstrap repeated sampling calculation C-index was used to evaluate the

29   model's calibration, and area under the curve (AUC) was used to evaluate the model discrimination ability.

30   **Results.** Multivariate logistic analysis showed that patients older than 50-year-old, dysphagia, refractory itching, and

31   elevated creatine kinase were independent risk factors for dermatomyositis associated with malignancy, while

32   interstitial lung disease was a protective factor. Based on this, we constructed a nomogram using the above-mentioned

33   five factors. The C-index was 0.780 (95% CI: 0.690-0.870) in the training cohort and 0.756 (95% CI: 0.618-0.893) in

34   the validation cohort, while the AUC value was 0.756 (95% CI: 0.600-0.833). Taken together, our nomogram showed

35   good calibration and was effective in predicting which dermatomyositis patients were at a higher risk of developing

36   malignant tumors.

37   **Keywords** Dermatomyositis, malignancy, predictor, nomogram, risk prediction model

38

39 **Introduction**

40   Dermatomyositis is a group of autoimmune diseases that mainly damage the skin and muscles and is often

41 accompanied by tumors and internal organ damage. Skin lesions are characterized by periorbital erythema, Gottron's

42 sign, poikiloderma and V-neck sign. Myositis often manifests as proximal muscle weakness, joint pain and dysphagia.

43 The relationship between dermatomyositis and malignancy was first reported by Stetz in 1916[1]. As a paraneoplastic

44 syndrome, tumors commonly associate with dermatomyositis, including nasopharyngeal cancer, breast cancer, thyroid

45 cancer, ovarian cancer and lung cancer and so on. The pathogenesis is reportedly related to the immune cross-reaction

46 between tumors and normal host tissues or the secretion of functional peptides and hormones[2]. Dermatomyositis

47 patients with underlying malignancy have a poorer prognosis compared to those without. It has been reported that the

48 incidence of malignancy in adults with dermatomyositis ranges from 23% to 45%[3-5]. The 5-year survival rate of

49 dermatomyositis patients with malignancy ranges from 51.8% to 74.2%[4, 6]. In addition, some studies have reported

50 that the incidence of malignancy in dermatomyositis is highest in the first year after diagnosis [7]. Therefore, it is

51 critical to predict the probable risk of malignancy in dermatomyositis patients early.

52   Recently, it has been reported that a variety of myositis-specific autoantibodies (MSAs) associated with tumors

53 has been found in patients with dermatomyositis, including transcriptional intermediary factor 1-gamma (TIF-1γ),

54 nuclear matrix protein (NXP-2), anti-small ubiquitin-like modifier activating enzyme (SAE), anti-3-hydroxy-3-

55 methylglutaryl-coenzyme A reductase (HMGCR), etc[8]. Among them, TIF1γ has the highest positive rate in

56 dermatomyositis patients with underlying malignancy[9], with about 60% to 80% of positive TIF-1 patients harboring

57 a malignancy[8]. Although TIF1γ shows a strong connection between malignancy and myositis, many hospitals have

58 not carried out TIF-γ1 testing clinically due to the high cost. In addition, a previous meta-analysis[10] has shown that

59 male dermatomyositis patients older than 45-year-old with dysphagia, cutaneous necrosis, cutaneous vasculitis, rapid

60   onset of myositis (<4 weeks), elevated creatine kinase (CK), elevated erythrocyte sedimentation rate (ESR), and

61   elevated C-reactive protein (CRP) were more likely to develop malignancy, while interstitial lung disease (ILD),

62   arthritis, Raynaud syndrome and the presence of anti-Jo-1 decreased that risk. However, to date, no quantitative

63   predictive model based on the above predictors has been established to help identify malignancy incidence in patients

64   with dermatomyositis.

65   Therefore, to that end, we established a clinical prediction model for diagnosing dermatomyositis with underlying

66   malignancy. Nomograms are generally used to transform complex regression equations into visual graphics, making

67   the predictive model more readable and convenient for patient evaluation. A score is assigned according to each

68   influencing factor's degree of contribution to the outcome of the variable. After which, the scores are added together

69   to obtain the total score. Finally, the predicted value of the individual outcome event is calculated through the function

70   conversion relationship between the total score and the probability of an outcome event [11, 12]. Our predictive model

71   was further verified both internally and externally to ensure good clinical reproducibility. To our knowledge, this is

72   the first nomogram constructed to predict the probability of malignancy in dermatomyositis patients.

73   **Materials & Methods**

74   **Patients**

75   Since this study was a retrospective study, all the patients included in the study had been discharged from the

76   hospital, and the signature of written consent from the patients could not be obtained. However, to obtain the patients'

77   consent, the researchers have contacted the patients in the study one by one by telephone and informed them of the

78   contents of the informed consent forms. Oral consent has been obtained, and the patients have authorized us to use the

79   data during their hospital stay in the study. The Ethics Committee of Sun Yat-sen Memorial Hospital, Sun Yat-sen

80   University, has approved the oral consent for this study instead of the written informed consent (SYSEC-KY-KS-

81   2020-038).

82   It was registered in the Chinese Clinical Trial Registry (Registration No. ChiCTR2000031286). This study

83   followed all relevant regulations in terms of data collection and storage. The clinical data of patients diagnosed with

84   dermatomyositis at Sun Yat-sen Memorial Hospital, Sun Yat-sen University, from January 2002 to December 2019

85   were collected from the hospital database.

86   The inclusion criteria were according to the diagnosis criteria of dermatomyositis proposed by Bohan and Peter

87   in 1975: (1) proximal symmetry of weak muscles in the extremities, with or without difficulty in swallowing and

88   respiratory muscle weakness; (2) elevated muscle enzymes; (3) electromyography showing myogenic changes; (4)

89   abnormal muscle biopsy; (5) characteristic cutaneous changes.

90   Exclusion criteria were as follows: (1) incomplete clinical data records and inadequate examinations; (2)

91   unconfirmed diagnosis of dermatomyositis; (3) malignancy occurred before the diagnosis of dermatomyositis; (4)

92   patients with overlapping syndrome, that is, combined other rheumatic immune diseases (such as systemic lupus

93   erythematosus, scleroderma, polymyositis, rheumatoid arthritis, etc.).

94   The patients were selected according to the inclusion and exclusion criteria. After a diagnosis of dermatomyositis,

95   they were divided into the malignancy and non-malignancy groups. Depending on the year of the first admission,

96   patients from 2002 to 2015 were designated into the training cohort, while patients from 2016 to 2019 were assigned

97   to the validation cohort.

98   **Data collection**

99   The following clinical data were collected: (1) general information of the patient: age, gender; (2) clinical

100   manifestations involving Gottron's sign, periungual erythema, poikiloderma, refractory itching, V-neck sign,

101   periorbital erythema, Raynaud's phenomenon, joint pain, proximal muscle weakness, and dysphagia; (3) laboratory

102   indicators: antinuclear antibodies (ANA), anti-Jo-1 antibodies, CK, lactate dehydrogenase (LDH), carbohydrate

103   antigen 125 (CA125), carbohydrate antigen 19-9 (CA19-9); (4) complications: malignancy, ILD, respiratory failure.

104   **Variables definition**

105   . Dermatomyositis patients with associated malignancy were diagnosed by pathological biopsy, including biopsy

106   after tumor resection, endoscopic biopsy, and lymph node aspiration. ILD was diagnosed by chest X-ray or high-

107   resolution CT (characterized by an increased lung density with a frosted glass-like appearance in bilateral lower lung

108   fields), pulmonary function testing, and lung biopsy. Respiratory failure refers to severe obstruction of pulmonary

109   ventilation and/or ventilation function caused by various reasons, leading to hypoxia with/without carbon dioxide

110   retention, with arterial blood gas values of PaO_2 below 60 mmHg, with or without a $PaCO_2$ value above 50 mmHg.

111   **Model Development**

112   According to the normal data range, the continuous variables in the predictors were converted into binary variables.

113   Then, SPSS ver. 22.0 (IBM Co., Armonk, NY, USA) was used to compare the composition of the basic data in the

114   training and validation cohort, using the χ2 test (or Fisher's exact test) and t-test (or Mann-Whitney U test) for

115   categorical and continuous variables, respectively. Univariate logistic regression was used to evaluate the relationship

116   between each independent variable and the occurrence of malignancy. The variables with significant differences ($P <$

117   0.1) were further incorporated into our multivariate logistic analysis to screen for independent predictors[14]. The

118   selected predictors were introduced into R ver. 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria;

119   http://www.r-project.org/), and a nomogram prediction model was constructed using the rms software package.

120   **Model validation**

121   Internal validation was performed using the bootstrap method for repeated sampling (1000 times). The calibration

122   of the nomogram was evaluated by the Concordance index (C-index). The calibration curve was analyzed by plotting

123   the predicted nomogram and the actual probability of malignancy in patients with dermatomyositis. The C-index of

124   the calibration curve ranged from 0.5 to 1. The closer it is to 1, the more accurate the model's prediction results are in

125   accordance with the actual situation. For external validation, dermatomyositis patients from January 2016 to December

126   2019 were selected according to the same inclusion and exclusion criteria. The receiver operating characteristic curve

127   (ROC) was drawn, and the area under the curve (AUC) was calculated to evaluate the model's discrimination ability.

128   The closer the AUC value is to 1, the better the model's discrimination is.

129   **Results**

130   **Patients characteristic**

131   A total of 289 patients with dermatomyositis were enrolled in this study. After excluding patients with incomplete

132   data, malignancy occurring before dermatomyositis, and patients with other rheumatoid immune diseases, a total of

133   240 cases were selected for further analysis, including 93 men and 147 women. The average age of the patients was

134   46.99 ± 18.17 years. Among them, 54 cases had malignancy. The top 3 malignant tumors were nasopharyngeal cancer

135   (37.0%), lung cancer (16.7%), breast cancer (13.0%) (Supplement table 1). All eligible patients were grouped by

136   the year of admission, 168 patients admitted from 2002 to 2015 were selected for our training cohort, and 72 patients

137   admitted to the hospital from 2016 to 2019 were picked for our validation cohort (Fig. 1). The ratio of the two groups

138   was 7:3. The demographic, clinical characteristics and experimental results of the training and validation cohorts were

139   similar (Table 1).

140   **Predictive factors for dermatomyositis patients with malignancy**

141   In the training cohort, univariate logistic regression was used to identify potential predictors of dermatomyositis

142   with malignancy (Table 2). When contrasting the malignant tumor group to the non-malignant tumor group, we found

143   that patients with dysphagia [odds ratio (OR)=4.224; 95% confidence interval (CI): 1.932-9.233; P<0.001], male

144   gender (OR=1.864; 95% CI: 0.909-3,780; P=0.084), poikiloderma (OR=2.241; 95% CI: 0.916-5.486; P=0.077),

145   elevated CK (OR=3.137; 95% CI: 1.521-6.467; P=0.002), refractory itching (OR=3.267; 95% CI: 1.274-8.378;

146   P=0.014), above 50 years of age (OR=2.200; 95% CI: 1.060-4.568; P=0.034) and elevated CA19-9 (OR=2.672; 95%

147   CI: 1.034-6.902; P=0.042) were more likely to develop malignancies. While patients with ILD (OR=0.440; 95% CI:

148   0.207-0.936; P=0.033) were less likely to have malignancies.

149   After further multivariate analysis (Table 2), we found that the male gender, poikiloderma and elevated CA19-9

150   could not independently predict malignancy in dermatomyositis patients. For the remaining predictors, patients above

151   50 yeard old (OR=3.534; 95% CI: 1.414-8.831; P=0.007), refractory itching (OR=4.642; 95% CI: 1.375-15.671;

152   P=0.013), dysphagia (OR=4.223; 95% CI: 1.617-11.023; P=0.003) , and elevated CK (OR=2.306; 95% CI: 1.003-

153   5.304; P=0.049) were risk factors for dermatomyositis patients with malignancy. On the other hand, ILD (OR=0.367;

154   95% CI: 0.147-0.913; P=0.031) was a protective factor.

155   **Development and validation of the predictive nomogram**

156   Based on the predictive factors selected by the univariate and multivariate logistic regression, a nomogram was

157   constructed to predict the probability of malignancy occurrence in patients with dermatomyositis (Fig. 2). The value

158   of each factor can be determined based on the intersection of the vertical line drawn from the variable to the point

159   axis, and then the total risk score was calculated by adding all the variable points. The probability of malignant

160   occurrence can be read directly on the total point axis. In addition, to facilitate the calculation of the probability of

161   dermatomyositis with underlying malignancy, we provided the corresponding table form of the nomogram prediction

162   model (Supplement Table 2), which provided the risk points of each factor and the corresponding probability to the

163   total risk points.

164   In the training cohort, the C-index of the nomogram was 0.780 (95% CI: 0.690-0.870). The calibration curve

165   showed a good consistency between predictions from the nomogram and the actual observations (Fig. 3A). The

166   performance of the nomogram was also evaluated in the validation cohort, with a C-index of 0.756 (95% CI: 0.618-

167   0.893) (Fig. 3B). The calibration curve also showed that the probability predicted by the nomogram was highly

168   compatible clinically. In addition, the calculated AUC was 0.756 (95% CI: 0.600-0.833), indicating that the model

169   has a good discrimination ability (Fig. 4).

170   **Discussion**

171   Dermatomyositis with underlying malignancy has a high incidence and appears concurrently or successively.

172   Malignancy is one of the triggering factors for dermatomyositis, which induces autoimmune mechanisms through

173   MSAs. It has been determined that certain MSAs are significantly associated with tumor-related dermatomyositis,

174   such as TIF-1γ, NXP-2, SAE and HMGCR. Malignancy induces the expression and secretion of abnormal proteins

175   (tumor-specific antigens), which are highly immunogenic and strongly cross-react with normal tissues. In addition,

176   malignancy can express normal host proteins (tumor-associated antigen, TAA). Because TAAs are not specific to

177   tumor cells, loss of tolerance to TAAs may cause the host to develop immunity against normal tissues, resulting in

178   autoimmunity[15]. The sequence of dermatomyositis immune activation is unknown and may result from excessive

179   complement activation[16]. Early diagnosis of malignancy significantly impacts prognosis, especially for tumor types

180   that lack specific indicators and are difficult to diagnose early on. Dermatomyositis is considered to be a paraneoplastic

181   syndrome, and most dermatomyositis patients have no other specific manifestations upon diagnosis. However,

182   malignancy is not the only triggering factor for patients with dermatomyositis. Therefore, screening malignant patients

183   with a high risk of dermatomyositis is of great significance for improving the early detection rate of tumors and

184   improving the tumor prognosis.

185   To guide clinical management strategies, this study established a risk prediction model for dermatomyositis

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186   patients with underlying malignancy and screened out five predictors, namely age, dysphagia, refractory itching, ILD

187   and elevated CK. Dysphagia, refractory itching, and elevated CK accounted for the higher scores in the predictive

188   model and were significantly associated with malignancy. These symptoms and the results of laboratory tests were

189   also related to dermatomyositis activity, indicating that immuno-inflammatory response was upregulated in vivo, and

190   the autoimmune antibody titers were increased, leading to tumor-associated immune pathways activation. Besides,

191   age also had a higher score in the prediction model. Almost all previous studies considered age to be a clear predictor,

192   which is consistent with the biological behavior of tumors. Consequently, it is recommended that dermatomyositis

193   patients over the age of 50 routinely undergo screening for tumors, including tumor-related history, physical

194   examination, age-appropriate tumor marker screening, and whole-body imaging (CT, MRI or MRI) PET-CT)

195   screening and even biopsy of suspicious lesions. ILD was found to be a protective factor for dermatomyositis

196   associated with malignancy. Dermatomyositis patients with concurrent ILD had a significantly lower risk of

197   developing malignancy, which is in line with the results of other highly credible clinical studies[10, 17-19]. ILD is

198   significantly related to the anti-MDA5 antibody (melanoma differentiation-associated gene 5, MDA5), especially

199   aggressive ILD with a poor prognosis. Compared with typical dermatomyositis patients, the degree of IFN-related

200   pathways activation in MDA5 positive patients was lighter, accompanied by a lower-activating state of STAT1,

201   leading to a down-regulation of NOS2 expression in Th1 macrophages. At the same time, it was observed that MDA5

202   positive dermatomyositis patients specifically expressed NOS2 in sarcoplasmic muscle fibers and co-localized with

203   the protective HP70 chaperone protein. These mechanisms suggest that ILD might play a role in tumor suppression[20].

204   However, the current negative correlation between ILD and tumors in patients with dermatomyositis warrants further

205   exploration.

206   In previous studies, a meta-analysis[10] comprehensively evaluated the risk factors and protective factors of

207   dermatomyositis associated with malignancy. There were several similarities and differences between the conclusions

208   of this article and previous ones. Herein, we reported that age, dysphagia, and refractory itching are risk predictors, in

209   line with the previous meta-analysis's conclusion. However, gender was not considered a predictor in this study;

210   although previous studies found the opposite. The meta-analysis had a lower OR value for gender as a risk factor

211   (OR=1.92, 95% CI: 1.49-2.48), indicating that the reliability of gender as a high-risk factor was uncertain. The

212   reliability of gender in epidemiology depends mainly on the number of cases, and thus, increasing the number of cases

213   may change the status of the gender in the risk prediction model. ESR, CRP, WBC and other laboratory tests were not

214   considered predictors, which might be due to the close relationship between laboratory tests levels and the patient's

215   current inflammation and immune status that tend to have large fluctuations throughout the course of the disease. A

216   retrospective study has shown that heliotrope rash and Gottron's sign are also risk factors for malignancy in

217   dermatomyositis patients [21], which might be related to positive anti-p155 antibody level. Anti-p155 positive

218   dermatomyositis patients have an increased risk of malignancy[22] and often have poikiloderma, Gottron's sign,

219   heliotrope rash, and V-neck sign[21]. However, our findings show that these vasculitis-related lesions are not related to

220   the onset of malignancy in patients with dermatomyositis, which might be due to the insufficient number of cases that

221   cannot reflect the statistical differences of these variables.

222   A nomogram clinical prediction model for dermatomyositis patients with underlying malignancy was established

223   for the first time based on 5 predictors. The prevalence of dermatomyositis is low, about 7-9/1,000,000[23], which

224   greatly limited the number of cases recruited for investigation. However, the internal and external calibration curves

225   showed consistency with clinical observations and had good predictive power. Our external verification did not use

226   participants from other institutions; instead, new participant data at a later period in the same database was used. This

227   verification method has been used before and conforms to the norm[24]. More importantly, the predictive indicators of

228 this model are easy to obtain and observe, which is beneficial to physicians and has great value for identifying

229 malignancy in patients with dermatomyositis.

230 Nevertheless, this study has several limitations: (1) The number of cases investigated was small since it was a

231 single-center study. (2) The south of China is in the subtropical zone, closer to the equator, and is different from other

232 regions in terms of climate and environment. Some studies suggested that multiple environmental factors can also

233 trigger chronic immune activation in patients with genetic susceptibilities, such as ultraviolet light and viral

234 infections[25]. Therefore, this study might be representative of the patient population in the south of China only. (3)

235 Cases with incomplete clinical data have been excluded leading to possible publication bias. (4) The median follow-

236 up length of patients with dermatomyositis was insufficient, which might lead to incomplete data acquisition since

237 some patients could have developed malignant tumors at a later stage of the disease. In the future, prospective studies

238 should be carried out with long-term follow-ups of dermatomyositis patients to obtain a more accurate incidence rate

239 of malignant tumors.

240 **Conclusions**

241 This study established a simple, intuitive, and practical nomogram risk prediction model for dermatomyositis

242 patients with underlying malignancy. Following internal and external validation, the model demonstrated a good

243 calibration and discrimination ability. Altogether, our nomogram has good clinical translational potential, possibly

244 helping physicians identify dermatomyositis patients at higher risk of developing malignancy. This could ultimately

245 lead to early tumor-related screening and follow-up of high-risk patients prolonging their clinical outcome

246 considerably. However, in order to optimize the model and improve the accuracy of prediction model, it is still

247 necessary to collect cases from multiple centers and different regions.

248 **Acknowledgment**

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250 **References**

251 1.   G. Stertz. Polymyositis. Berl Klin Wochenschr 1916, 53: 489.

252 2.   Pelosof L. C., Gerber D. E. Paraneoplastic syndromes: an approach to diagnosis and treatment. Mayo Clin Proc

253 2010, 85(9): 838-854.

254 3.   Maoz C. R., Langevitz P., Livneh A., Blumstein Z., Sadeh M., Bank I., Gur H., Ehrenfeld M. High incidence of

255 malignancies in patients with dermatomyositis and polymyositis: an 11-year analysis. Semin Arthritis Rheum 1998,

256 27(5): 319-324.

257 4.   Fang Y. F., Wu Y. J., Kuo C. F., Luo S. F., Yu K. H. Malignancy in dermatomyositis and polymyositis: analysis

258 of 192 patients. Clin Rheumatol 2016, 35(8): 1977-1984.

259 5.   Requena C., Alfaro A., Traves V., Nagore E., Llombart B., Serra C., Martorell A., Guillen C., Sanmartin O.

260 Paraneoplastic dermatomyositis: a study of 12 cases. Actas Dermosifiliogr 2014, 105(7): 675-682.

261 6.   Kim B. M., Kim S. H., Kim D. I., Shin Y. S., Suh S. H., Kim D. J., Park S. I., Park K. Y., Ahn S. S. Outcomes

262 and prognostic factors of intracranial unruptured vertebrobasilar artery dissection. Neurology 2011, 76(20): 1735-

263 1741.

264 7.   Chen D., Yuan S., Wu X., Li H., Qiu Q., Zhan Z., Ye Y., Lian F., Liang L., Xu H., Yang X. Incidence and

265 predictive factors for malignancies with dermatomyositis: a cohort from southern China. Clin Exp Rheumatol 2014,

266 32(5): 615-621.

267 8.   Trallero-Araguas E., Labrador-Horrillo M., Selva-O'Callaghan A., Martinez M. A., Martinez-Gomez X., Palou

268 E., Rodriguez-Sanchez J. L., Vilardell-Tarres M. Cancer-associated myositis and anti-p155 autoantibody in a series

269   of 85 patients with idiopathic inflammatory myopathy. Medicine (Baltimore) 2010, 89(1): 47-52.

270   9.   Hida A., Yamashita T., Hosono Y., Inoue M., Kaida K., Kadoya M., Miwa Y., Yajima N., Maezawa R., Arai S.,

271   Kurasawa K., Ito K., Shimada H., Iwanami T., Sonoo M., Hatanaka Y., Murayama S., Uchibori A., Chiba A., Aizawa

272   H., Momoo T., Nakae Y., Sakurai Y., Shiio Y., Hashida H., Yoshizawa T., Sakiyama Y., Oda A., Inoue K., Takeuchi

273   S., Iwata N. K., Date H., Masuda N., Mikata T., Motoyoshi Y., Uesaka Y., Maeda M. H., Nakashima R., Tsuji S.,

274   Kwak S., Mimori T., Shimizu J. Anti-TIF1-gamma antibody and cancer-associated myositis: A clinicohistopathologic

275   study. Neurology 2016, 87(3): 299-308.

276   10.   Lu X., Yang H., Shu X., Chen F., Zhang Y., Zhang S., Peng Q., Tian X., Wang G. Factors predicting malignancy

277   in patients with polymyositis and dermatomyostis: a systematic review and meta-analysis. PLoS One 2014, 9(4):

278   e94128.

279   11.   Balachandran V. P., Gonen M., Smith J. J., DeMatteo R. P. Nomograms in oncology: more than meets the eye.

280   Lancet Oncol 2015, 16(4): e173-180.

281   12.   Iasonos A., Schrag D., Raj G. V., Panageas K. S. How to build and interpret a nomogram for cancer prognosis.

282   J Clin Oncol 2008, 26(8): 1364-1370.

283   13.   Bohan A., Peter J. B. Polymyositis and dermatomyositis (first of two parts). N Engl J Med 1975, 292(7): 344-

284   347.

285   14.   Collins G. S., Reitsma J. B., Altman D. G., Moons K. G. Transparent reporting of a multivariable prediction

286   model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. BMJ 2015, 350: g7594.

287   15.   Adler B. L., Christopher-Stine L. Triggers of inflammatory myopathy: insights into pathogenesis. Discov Med

288   2018, 25(136): 75-83.

289   16.   DeWane M. E., Waldman R., Lu J. Dermatomyositis: Clinical features and pathogenesis. J Am Acad Dermatol

290   2020, 82(2): 267-281.

291   17.   Wang J., Guo G., Chen G., Wu B., Lu L., Bao L. Meta-analysis of the association of dermatomyositis and

292   polymyositis with cancer. Br J Dermatol 2013, 169(4): 838-847.

293   18.   Lega J. C., Fabien N., Reynaud Q., Durieu I., Durupt S., Dutertre M., Cordier J. F., Cottin V. The clinical

294   phenotype associated with myositis-specific and associated autoantibodies: a meta-analysis revisiting the so-called

295   antisynthetase syndrome. Autoimmun Rev 2014, 13(9): 883-891.

296   19.   Ikeda S., Arita M., Misaki K., Mishima S., Takaiwa T., Nishiyama A., Ito A., Furuta K., Yokoyama T., Tokioka

297   F., Noyama M., Yoshioka H., Ishida T. Incidence and impact of interstitial lung disease and malignancy in patients

298   with polymyositis, dermatomyositis, and clinically amyopathic dermatomyositis: a retrospective cohort study.

299   Springerplus 2015, 4: 240.

300   20.   Allenbach Y., Leroux G., Suarez-Calvet X., Preusse C., Gallardo E., Hervier B., Rigolet A., Hie M., Pehl D.,

301   Limal N., Hufnagl P., Zerbe N., Meyer A., Aouizerate J., Uzunhan Y., Maisonobe T., Goebel H. H., Benveniste O.,

302   Stenzel W., French Myositis Network. Dermatomyositis With or Without Anti-Melanoma Differentiation-Associated

303   Gene 5 Antibodies: Common Interferon Signature but Distinct NOS2 Expression. Am J Pathol 2016, 186(3): 691-

304   700.

305   21.   Targoff I. N., Mamyrova G., Trieu E. P., Perurena O., Koneru B., O'Hanlon T. P., Miller F. W., Rider L. G.,

306   Childhood Myositis Heterogeneity Study Group, International Myositis Collaborative Study Group. A novel

307   autoantibody to a 155-kd protein is associated with dermatomyositis. Arthritis Rheum 2006, 54(11): 3682-3689.

308   22.   Trallero-Araguas E., Rodrigo-Pendas J. A., Selva-O'Callaghan A., Martinez-Gomez X., Bosch X., Labrador-

309   Horrillo M., Grau-Junyent J. M., Vilardell-Tarres M. Usefulness of anti-p155 autoantibody for diagnosing cancer-

310   associated dermatomyositis: a systematic review and meta-analysis. Arthritis Rheum 2012, 64(2): 523-532.

311   23.   Sunderkotter C., Nast A., Worm M., Dengler R., Dorner T., Ganter H., Hohlfeld R., Melms A., Melzer N., Rosler

312   K., Schmidt J., Sinnreich M., Walter M. C., Wanschitz J., Wiendl H. Guidelines on dermatomyositis--excerpt from

313   the interdisciplinary S2k guidelines on myositis syndromes by the German Society of Neurology. J Dtsch Dermatol

314   Ges 2016, 14(3): 321-338.

315   24.   Moons K. G., Altman D. G., Reitsma J. B., Ioannidis J. P., Macaskill P., Steyerberg E. W., Vickers A. J.,

316   Ransohoff D. F., Collins G. S. Transparent Reporting of a multivariable prediction model for Individual Prognosis or

317   Diagnosis (TRIPOD): explanation and elaboration. Ann Intern Med 2015, 162(1): W1-73.

318   25.   Love L. A., Weinberg C. R., McConnaughey D. R., Oddis C. V., Medsger T. A., Jr., Reveille J. D., Arnett F. C.,

319   Targoff I. N., Miller F. W. Ultraviolet radiation intensity predicts the relative distribution of dermatomyositis and anti-

320   Mi-2 autoantibodies in women. Arthritis Rheum 2009, 60(8): 2499-2504.

321 **Table 1** Characteristics of patients with dermatomyositis

Characteristic	Training cohort (n=168)		Validation cohort (n=72)		P
	N	Percent (%)	N	Percent (%)	
Basic information					
Age (years), mean ± SD	48.09 ± 18.69		44.43 ± 16.73		0.153
Sex					0.977
Male	65	38.7	28	38.9	
Female	103	61.3	44	61.1	
Clinical manifestation					
Gottron's sign					0.167
yes	84	50.0	43	59.7	
no	84	50.0	29	40.3	
Periungual erythema					0.792
yes	19	11.3	9	12.5	
no	149	88.7	63	87.5	
Poikiloderma					0.019
yes	47	28.0	10	13.9	
no	121	72.0	62	86.1	
Refractory itching					0.562
yes	21	12.5	11	15.3	
no	147	87.5	61	84.7	
V-neck sign					0.842
yes	70	41.7	31	43.1	
no	98	58.3	41	56.9	
Periorbital erythema					0.185
yes	113	67.3	42	58.3	
no	55	32.7	30	41.7	
Raynaud's phenomenon					0.778
yes	8	4.8	4	5.6	
no	160	95.2	67	94.4	
Joint pain					0.258

yes	23	13.7	14	19.4	
no	145	86.3	58	80.6	
Proximal muscle weakness					0.829
yes	119	70.8	50	69.4	
no	49	29.2	22	30.6	
Dysphagia					0.837
yes	37	22.0	15	20.8	
no	131	78.0	57	79.2	
Complication					
Malignant tumor					0.157
yes	42	25.0	12	16.7	
no	126	75.5	60	83.3	
Interstitial pneumonia					0.411
yes	72	42.9	35	48.6	
no	96	57.1	37	51.4	
Respiration failure					0.205
yes	30	17.9	18	25.0	
no	138	82.1	54	75.0	
Laboratory values					
CK (U/L)					0.058
≥198	69	41.1	20	27.8	
<198	99	58.9	52	72.2	
LDH (U/L)					0.104
≥300	103	61.3	36	50.0	
<300	65	38.7	36	50.0	
ANA					0.862
Positive	103	61.3	45	62.5	
Negative	65	38.7	27	37.5	
Anti-Jo-1					0.004
Positive	4	2.4	8	11.1	

Negative	164	97.6	64	88.9	
CA125(U/ml)					0.375
≥35	15	8.9	4	5.6	
<35	153	91.1	68	94.4	
CA19-9(U/ml)					0.200
≥37	21	12.6	5	6.9	
<37	146	87.4	67	93.1	

322   CK: creatine kinase; LDH: lactate dehydrogenase; ANA: antinuclear antibody; CA125:carbohydrate antigen

323   125; CA19-9: carbohydrate antigen 19-9.

Table 2 Univariate and multivariate analysis of risk factors in training cohort

Factors	Univariate		Multivariate	
	P	OR(95% CI)	P	OR (95% CI)
Age≥50y	0.034†	2.200 (1.060, 4.568)	0.007*	3.534 (1.414, 8.831)
Sex	0.084†	1.864 (0.909, 3.780)	0.180	1.804(0.761,4.276)
Gottron's sign	0.286	0.682 (0.337,1.379)		
Periochia erythema	0.888	1.081 (0.365, 3.205)		
Poikiloderma	0.077†	2.241(0.916, 5.486)	0.051	2.890 (0.994, 8.407)
Refractory itching	0.014†	3.267 (1.274, 8.378)	0.013*	4.642 (1.375, 15.671)
V-neck sign	0.857	1.067 (0.527, 2.163)		
Periorbital erythema	0.507	1.295 (0.603, 2.781)		
Raynaud's phenomenon	>0.999	<0.001		
Joint pain	0.165	0.408 (0.115, 1.449)		
Proximal muscle weakness	0.769	0.892 (0.417, 1.908)		
Dysphagia	<0.001†	4.224 (1.932, 9.233)	0.003*	4.223 (1.617, 11.023)
Interstitial pneumonia	0.033†	0.440 (0.207, 0.936)	0.031*	0.367 (0.147, 0.913)
Respiration failure	0.250	0.546 (0.195, 1.531)		
CK≥198U/L	0.002†	3.137 (1.521, 6.467)	0.049*	2.306(1.003,5.304)
LDH≥300U/L	0.784	0.905 (0.443, 1.847)		
ANA(+)	0.316	0.696 (0.343, 1.412)		
Anti-Jo-1(+)	>0.999	<0.001		
CA125≥35 U/ml	0.876	1.100 (0.331, 3.660)		
CA19-9≥37 U/ml	0.042†	2.672 (1.034, 6.902)	0.319	1.811 (0.563, 5.824)

OR, odds ratio; CI, confidence interval.

†*P*<0.1,*P < 0.05, statistically significant difference.

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Figure 1

Figure 1 Flow chart for cases selection
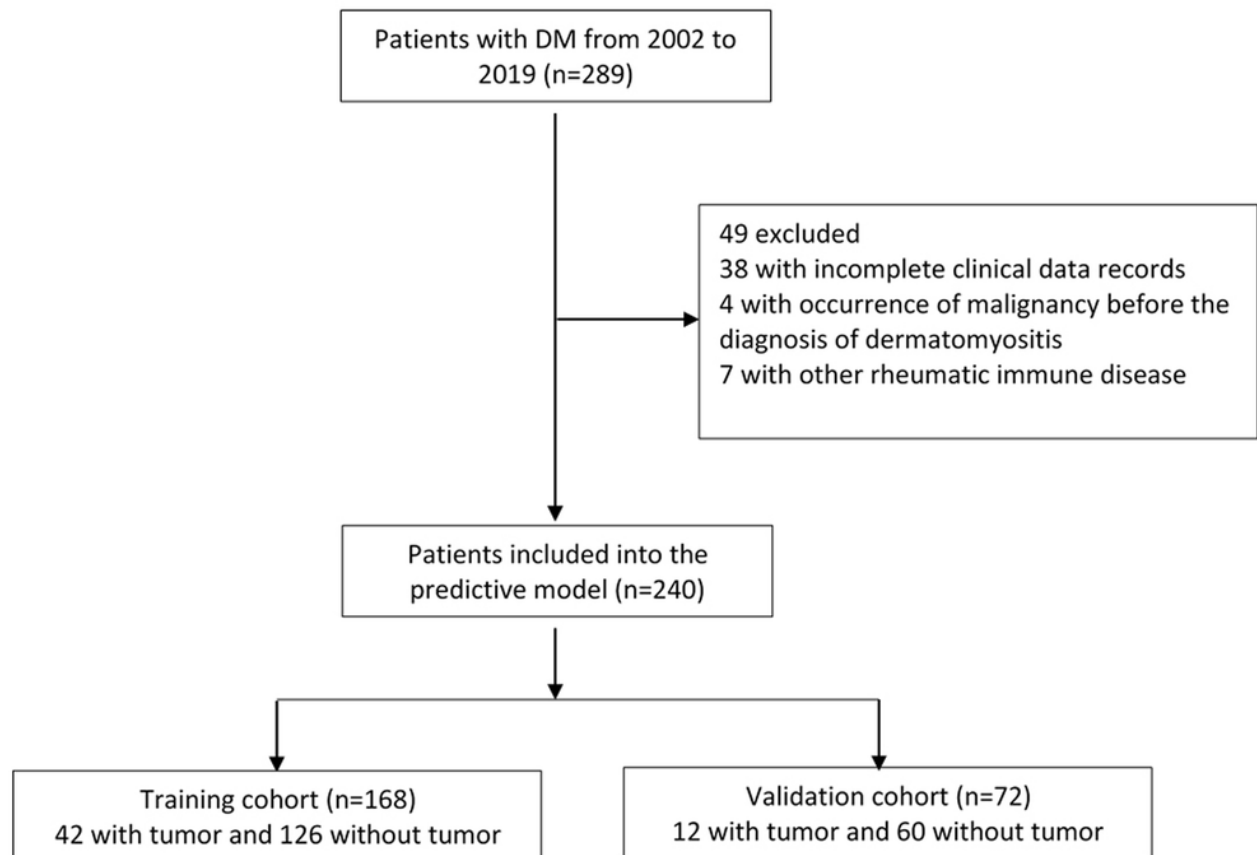
Figure 2

Figure 2 Nomogram for individualized prediction of malignancy in patients with dermatomyositis
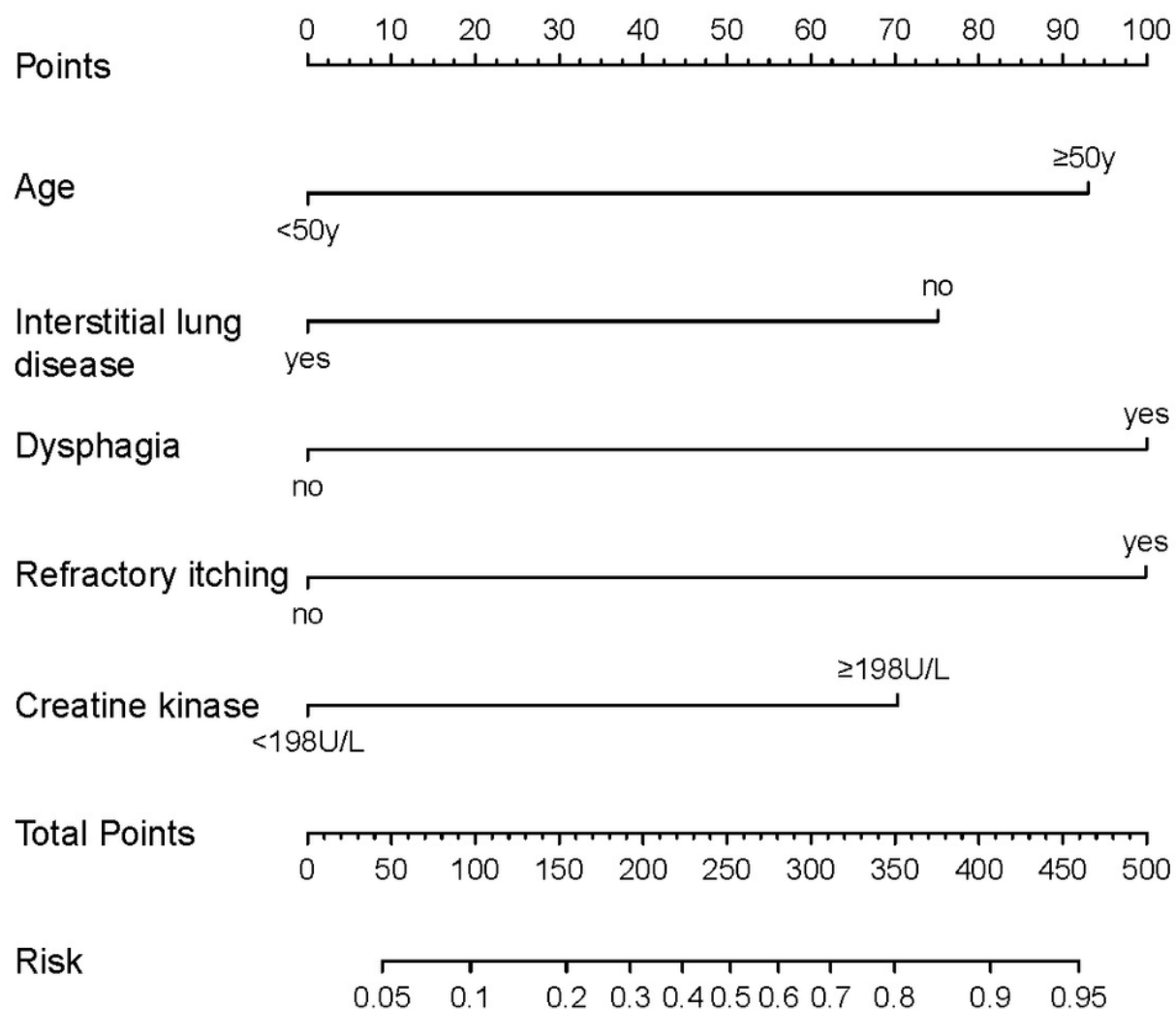
Figure 3

Figure 3 Calibration curve comparing predicted and actual probabilities of dermatomyositis with malignancy in the training cohort (A) and in the validation cohort (B).
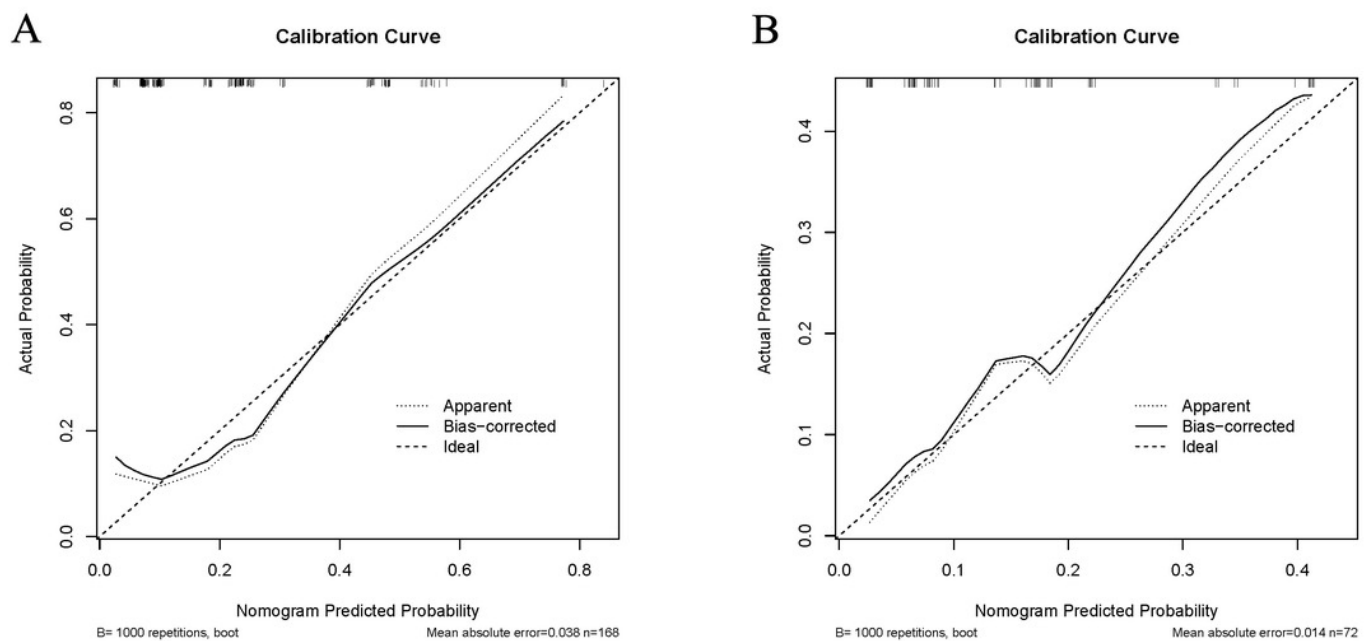
Figure 4

Figure 4 Receiver under the operator characteristic (ROC) curve for the test accuracy in the validation cohort.