

## Article

# Evaluating the Risk Factors of Post Inflammatory Hyperpigmentation Complications with Nd-YAG Laser Toning Using LASSO-Based Algorithm

Chao-Hong Liu <sup>1,2</sup>, Chin-Shiuh Shieh <sup>1</sup> , Tai-Lin Huang <sup>3</sup>, Chih-Hsueh Lin <sup>1</sup>, Pei-Ju Chao <sup>1,4</sup>, Yu-Jie Huang <sup>4</sup>, Hsiao-Fei Lee <sup>1,4</sup>, Shyh-An Yeh <sup>1</sup>, Chin-Dar Tseng <sup>1</sup> , Jia-Ming Wu <sup>5</sup>, Stephen Wan Leung <sup>1,6</sup> and Tsair-Fwu Lee <sup>1,4,7,\*</sup> 

<sup>1</sup> Department of Electronics Engineering, National Kaohsiung University of Science and Technology, Kaohsiung 80778, Taiwan; y4509@yuanhosp.com.tw (C.-H.L.); csshie@gmail.com (C.-S.S.); cslin@nkust.edu.tw (C.-H.L.); pjchao99@gmail.com (P.-J.C.); hsiaofeilee@gmail.com (H.-F.L.); sayeh@outlook.com (S.-A.Y.); 1102405111@gm.kuas.edu.tw (C.-D.T.); lwan@ms36.hinet.net (S.W.L.)

<sup>2</sup> Department of Dermatology, Kaohsiung Yuan's General Hospital, Kaohsiung 80249, Taiwan

<sup>3</sup> Department of Hematology and Oncology, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung 83342, Taiwan; victorhtl@yahoo.com.tw

<sup>4</sup> Department of Radiation Oncology, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung 83342, Taiwan; yjhuang@adm.cgmh.org.tw

<sup>5</sup> Department of Biomedicine Engineering, Chengde Medical University, Chengde City 067000, China; jiaming.wu@chmsc.com

<sup>6</sup> Department of Radiation Oncology, Kaohsiung Yuan's General Hospital, Kaohsiung 80249, Taiwan

<sup>7</sup> College of Biomedical Engineering, Kaohsiung Medical University, Kaohsiung 80708, Taiwan

\* Correspondence: tflee@nkust.edu.tw; Tel.: +886-73814526 (ext. 15657); Fax: +886-73811182

Received: 1 January 2020; Accepted: 16 March 2020; Published: 18 March 2020



**Abstract:** The neodymium-doped yttrium aluminum garnet (Nd-YAG) laser is used for removal of pigmented skin patches and rejuvenation of skin. However, complications such as hyperpigmentation, hypopigmentation, and petechiae can occur after frequent treatments. Therefore, identifying the risk factors for such complications is important. The development of a multivariable logistic regression model with least absolute shrinkage and selection operator (LASSO) is needed to provide valid predictions about the incidence of post inflammatory hyperpigmentation complication probability (PIHCP) among patients treated with Nd-YAG laser toning. A total of 125 female patients undergoing laser toning therapy between January 2014 and January 2016 were examined for post-inflammatory hyperpigmentation (PIH) complications. Factor analysis was performed using 15 potential predictive risk factors of PIH determined by a physician. The LASSO algorithm with cross-validation was used to select the optimal number of predictive risk factors from the potential factors for a multivariate logistic regression PIH complication model. The optimal number of predictive risk factors for the model was five: immediate endpoints of laser (IEL),  $\alpha$ -hydroxy acid (AHA) peels, Fitzpatrick skin phototype (FSPT), acne, and melasma. The area under the receiver operating characteristic curve (AUC) was 0.79 (95% CI, 0.70–0.88) in the optimal model. The overall performance of the LASSO-based PIHCP model was satisfactory based on the AUC, Omnibus, Nagelkerke  $R^2$ , and Hosmer–Lemeshow tests. This predictive risk factor model is useful to further optimize laser toning treatment related to PIH. The LASSO-based PIHCP model could be useful for decision-making.

**Keywords:** laser toning; post inflammatory hyperpigmentation; LASSO; risk factors; PIHCP

## 1. Introduction

Laser toning with a low-fluence 1064 nm Q-switched neodymium-doped yttrium aluminum garnet (Nd-YAG) laser can be used for removal of pigmented skin patches and rejuvenation of skin [1,2]. Laser toning involves multiple passes of a low-fluence Q-switched Nd-YAG laser used for treatment of facial hyperpigmentation and skin rejuvenation. However, the side effects of rebound post-inflammatory hyperpigmentation (PIH) are common after laser toning treatment. PIH is an acquired hyperpigmentation at the sites of previous skin inflammation, injuries, irritants, or allergic dermatitis, and cosmetic procedures such as chemical peeling and laser treatment.

Wanner et al. pointed out that immediate endpoints of laser (IEL) is an indicator of laser tissue response and PIH is caused by inflammation [3,4]. Song et al. reported that the increase in epidermal pigmentation after laser irradiation is related to the increased expression of certain inflammatory cytokines, suggesting that they may be the cause of PIH induction [5]. Narumol et al. found that the strength of PIH is determined by inherent skin color, inflammatory conditions, and melanocyte stability [6]. However, the authors used a different method than previous authors.

Such complications not only reduce the quality of life but also decrease patient compliance, and efforts should therefore be directed toward their prevention. The main risk factors related to these complications are likely to include several clinical factors. The risk of treatment complications should be analyzed by multivariate regression including several predictor variables. Identifying the main potential risk factors for complications is important for improving the decision-making process.

The development of an optimal multivariate logistic regression model requires determination of the optimal number of predictive factors that should be included. Therefore, a predictive model must be developed to analyze the possible risk factors of complications.

Xu et al. [7–9] introduced the (least absolute shrinkage and selection operator (LASSO) algorithm for multivariate regression modeling. In addition to its simple use, LASSO has a number of advantages including: (1) variable selection, (2) coefficient shrinkage, (3) consideration of multicollinearity, and (4) low mean squared error (MSE) values [7–9].

In this study, regularization and shrinkage techniques were used for LASSO factor selection, which limit the weight of regression to limit the complexity of the model and overcome overfitting problems. Different  $\lambda$  values (tuning parameter) have different shrinkage effects, so we used cross-validation to verify the model's execution results at different  $\lambda$  values. In our previous studies, we successfully used the LASSO-based normal tissue complication probability (NTCP) model to predict the incidence of xerostomia among head-and-neck squamous cell carcinoma (HNSCC) and nasopharyngeal carcinoma (NPC) patients treated with intensity-modulated radiotherapy (IMRT) [10] and other NPC patients treated with helical tomotherapy (HT) [11].

To the best of our knowledge, no previous reports have been published of risk assessment tools for identifying risk factors of PIH after laser toning or non-ablative skin rejuvenation using the LASSO-based algorithm. LASSO was used to determine the important risk factors for complications. Statistical methods were used to evaluate the pros and cons of the model. We built a LASSO-based multivariate logistic regression model to predict the incidence of PIH complications associated with Nd-YAG laser toning in Asian patients. This study is unique and innovative.

## 2. Methods

### 2.1. Samples

This retrospective study was designed to determine clinical factors relevant to female Asian patients undergoing facial laser toning therapy. A total of 125 samples from women who underwent laser toning therapy between January 2014 and January 2016 at Kaohsiung Yuan's General Hospital were enrolled in this study. Table 1 presents the treatment parameters and characteristic features of the enrolled samples.

**Table 1.** Sample characteristics.

Factors	(n = 125) Value-x (%)
Age (years)	
Mean	47.18
Range	21.00–77.00
<51	83 (66.4)
51–60	25 (20.0)
61–70	13 (10.4)
>71	4 (3.2)
FSPT	
Type III	85 (68.0)
Type IV	27 (21.6)
Type V	13 (10.4)
Melasma	
No	81 (64.8)
Yes	44 (35.2)
Acne	
No	108 (86.4)
Yes	17 (13.6)
ZN	
No	115 (92.0)
Yes	10 (8.0)
Lentigines	
No	45 (36.0)
Yes	80 (64.0)
Pores	
No	85 (68.0)
Yes	40 (32.0)
LD	
<750	28 (22.4)
750–850	62 (49.6)
>850	35 (28.0)
Laser Mode	
Fractional	40 (32.0)
Zoom	85 (68.0)
IEL	
Erythema	21 (16.8)
Petechiae	95 (76.0)
E mild P	9 (7.2)
PIH	
No	104 (83.2)
Yes	21 (16.8)

Abbreviations: FSPT: Fitzpatrick skin phototype; ZN: Zygomatic Nevus; LD: Laser Dosage; F: Fractional; Z: Zoom; Z+F: Zoom and Fractional; IEL: Immediate Endpoints of Laser; E: Erythema; P: Petechiae; E mild P: Erythema mild Petechiae; PIH: Post Inflammatory Hyperpigmentation; Data from Fitzpatrick RE [12].

## 2.2. Treatment

Laser toning was performed using a Q-switched Nd-YAG laser (Helios II; LaserOptek, Sungnam-si, Korea), with a spot size of 6–8 mm and fluence of 2.1–3.5 J/cm<sup>2</sup> at 8–10 Hz. Multiple laser passes were delivered to achieve the clinical endpoint of mild erythema. The laser was applied to the whole face with 3000–5000 shots in a single session. The number of treatment sessions varied according to the patient's needs. All patients were women and received full-face treatment. PIH was diagnosed based on clinical findings and history-taking during each toning session.

### 2.3. Post-Inflammatory Hyperpigmentation Complications

PIH is a hyperpigmentation disorder resulting from cutaneous inflammation due to acquired inflammatory skin disease, contact with allergens or irritants, cosmetic procedures, or traumatic skin injury [1,6]. Clinical visual assessment by comparison with the normal skin color (at baseline) and history-taking are usually performed with PIH patients [6]. In the present study, the complications were evaluated by the same physician according to their professional experience and defined as PIH after treatment with laser toning. A full-face assessment was performed for each patient before the first treatment.

### 2.4. Predictive Risk Factors

Initially, 15 candidate predictive risk factors were analyzed for each patient, i.e., age, intense pulse light (IPL),  $\alpha$ -hydroxy acid (AHA) peels, sonophoresis, skin care, HELIOS II treatment frequency, laser dosage (LD), melasma, Fitzpatrick skin phototype (FSPT), zygomatic nevus (ZN), lentigines, acne, pores, laser mode (LM), and immediate endpoints of laser (IEL). The characteristics of the initial candidate risk factors for PIH complication probability (PIHCP) modeling are shown in Table 2.

**Table 2.** Predictive factors in the post inflammatory hyperpigmentation dataset.

No.	Factors	Range or Classification	Median or Frequency	Correlation
1	Age	21–77	46	−0.001
2	IPL	0–10	0	0.197
3	AHA Peels	0–11	0	0.458
4	Sonophoresis	0–41	0	0.175
5	Skin Care	0–96	0	−0.129
6	TF	2–28	6	−0.018
7	LD	600–1000	750	−0.002
8	Melasma	0, 1 *	81, 44	0.969
9	FSPT	0, 1, 2	85, 27, 13	# <sup>1</sup>
10	ZN	0, 1 *	115, 10	−1.271
11	Lentigines	0, 1 *	45, 80	−0.378
12	Acnes	0, 1 *	109, 16	1.052
13	Pores	0, 1 *	85, 40	0.773
14	LM	0, 1 *	85, 40	1.431
15	IEL	0, 1, 2	95, 21, 9	# <sup>2</sup>

Abbreviation: IPL: intense pulse light; AHA Peels:  $\alpha$ -hydroxyl acid peels; TF: HELIOS II Treatment Frequency; LD: Laser Dosage; FSPT: Fitzpatrick skin phototype; ZN: Zygomatic Nevus; LM: Laser Mode; IEL: Immediate Endpoints of Laser; \* 0 = No, 1 = Yes; #<sup>1</sup>: F(0) = 0, F(1) = −1.533, F(2) = −1.175; #<sup>2</sup>: I(0) = 0, I(1) = −2.379, I(2) = −0.615.

### 2.5. PIHCP Evaluation (LASSO)

To determine the optimal number of potential predictive risk factors for the PIHCP model, the LASSO process was performed with cross-validation. PIHCP predictive values for each patient were calculated using the following formula [13], as outlined in our previous reports [10,14,15]:

$$PIHCP = \frac{1}{1 + e^{-S}} \text{ where } S = \beta_0 + \sum_{i=1}^n \beta_i \cdot x_i \quad (1)$$

where  $\beta_i$  is the regression coefficient,  $x_i$  represents the different predictive factors,  $n$  is the number of predictive factors in the model, and  $\beta_0$  is a constant coefficient.

The details of the LASSO-based model were presented in previous reports [7,8,14,16]. The following equation was used to identify the predictive factors and shrink the coefficients:

$$\operatorname{argmin}_{\beta} \|Y - X\beta\|^2 \text{ subject to } \|\beta\| = \sum_{j=0}^d |\beta_j| \leq t \quad (2)$$

where  $t$  represents the tuning parameters that can be determined by cross-validation and  $d$  indicates the number of variables selected. The details were reported previously [7,14,17].

An online MATLAB (MathWorks, Natick, MA, USA) package (LASSOGLM function) was downloaded and applied to fit the LASSO model on a HP Workstation Z640 (Hewlett-Packard, US). The LASSO method was performed with cross-validation (10 times) and the parameters ( $\lambda$  and  $\alpha$  values) were set based on the previous studies [3,4,18]. The default settings used for  $\lambda$  and  $\alpha$  (the elasticnet mixing parameter) were set to 1. In this study, the PIHCP probability model was derived from multiple logistic regression. In medical research, dependent variables are often referred to as outcome variables; independent variables are risk factors. The relevant details can be found in previous studies [10,14].

The system's performance measures were tested using the Nagelkerke  $R^2$  and Omnibus tests, scaled Brier score, area under the receiver operating characteristic curve (AUC), Hosmer–Lemeshow (HL) test, and negative predictive value (NPV) [15,19,20]. The data were processed using SPSS Statistics 19 (SPSS Inc., Chicago, IL, USA) and MATLAB R2013a (MathWorks, Natick, MA, USA). In all analyses,  $p < 0.05$  was taken to indicate statistical significance.

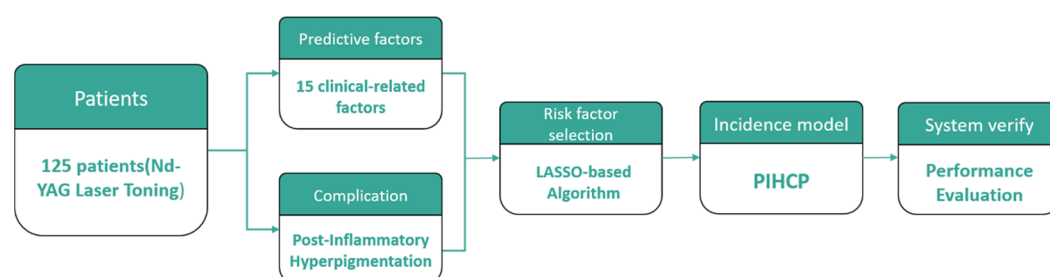
### 3. Results

Figure 1 shows the processing flow chart. PIH side effects after laser toning were reported by 16.8% of the patients ( $n = 21$ ) (Table 1). The average age of the patients was 47.18 years and ranged from 21 to 77 years. The FSPTs were as follows: FSPT III, 85 patients (68%); FSPT IV, 27 patients (22%); and FSPT V, 13 patients (10%). The LASSO algorithm was applied to determine the most important predictors of PIH complications. The factor rankings and LASSO trace plot of candidate predictors are shown in Figure 2A,B.

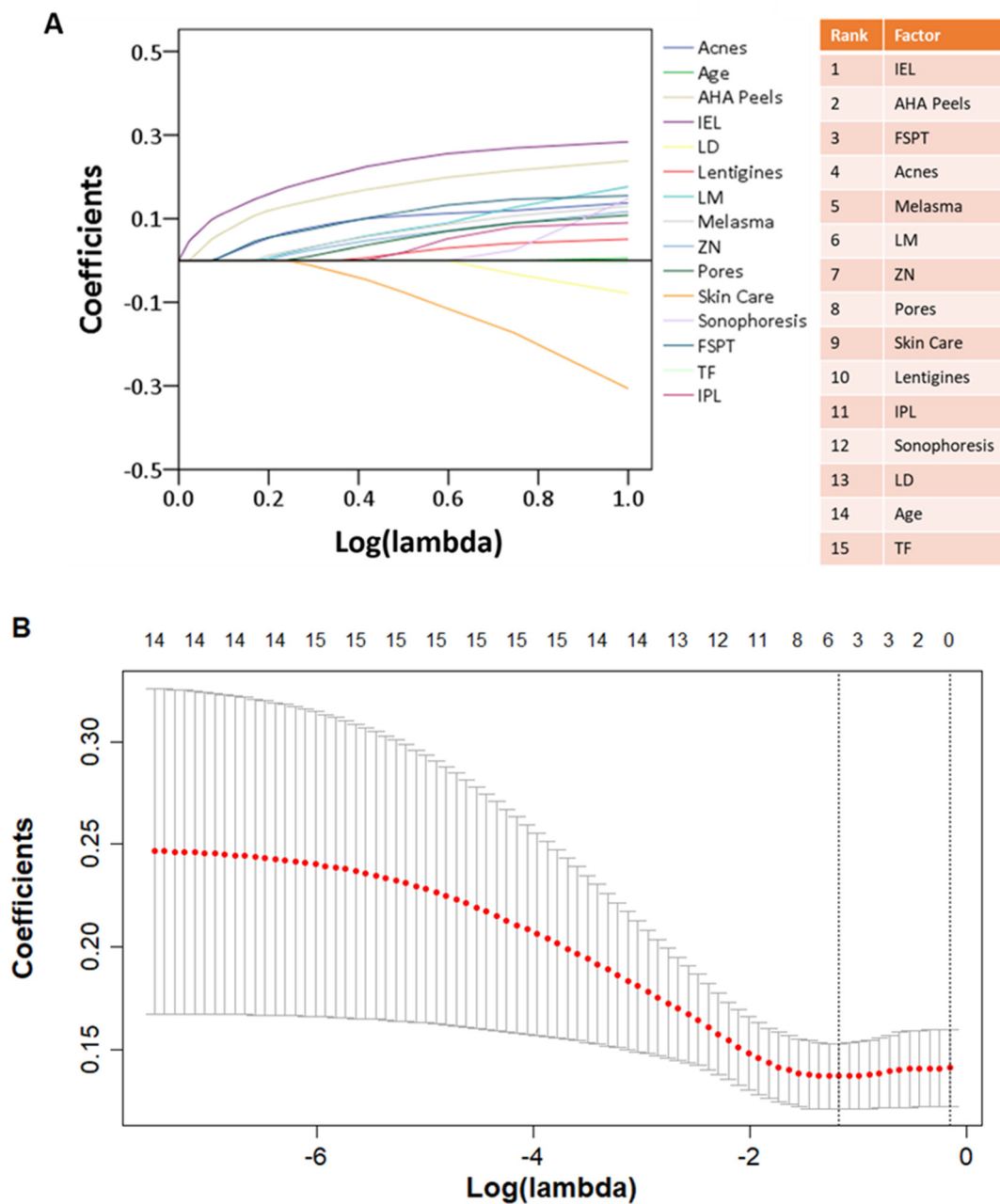
Figure 2A shows the LASSO trace plot of predictive factors and predictive factors ranking list. The selected factors were obtained by LASSO. According to their absolute values, the factors were IEL, AHA peel, FSPT, acne, and melasma. The higher the absolute value, the later the coefficient becomes zero, indicating that the factor is more important. Except for these five factors, the coefficients of the other factors were all 0, which were excluded by LASSO. Figure 2B shows the cross-validated mean squared error bars of the LASSO fit. The minimum error bar and with the higher AUC value indicates the number of factors selected [10,14].

The optimal number of risk factors for PIH complications selected by LASSO, with cross-validation, was five: IEL, AHA peel, FSPT, acne, and melasma.

For the optimal model of each individual patient, the PIHCP value was obtained using the formula in Equation (1), where  $S = 3.29 + (\text{IEL corresponding value}) + (\text{AHA corresponding value}) + (\text{FSPT corresponding value}) + (\text{acne corresponding value}) + (\text{melasma corresponding value})$ . The coefficients for the LASSO-based PIHCP model are shown in Table 3.



**Figure 1.** Processing flow chart for the LASSO-based PIHCP model. Abbreviations: LASSO: the least absolute shrinkage and selection operator algorithm; PIHCP: Post Inflammatory Hyperpigmentation complication probability; Nd-YAG: neodymium-doped yttrium aluminum garnet.



**Figure 2.** (A) LASSO trace plot of predictive factors and predictive factors ranking list. (B) The cross-validated mean squared error bars of the LASSO fit. Abbreviations: IEL: Immediate Endpoints of Laser; FSPT: Fitzpatrick skin phototype; AHA:  $\alpha$ -hydroxy acid; LM: Laser Mode; ZN: Zygomatic Nevus; IPL: intense pulse light; LD: Laser Dosage; TF: Treatment Frequency; X axis: Beta; Y axis: Coefficients; LASSO: the least absolute shrinkage and selection operator algorithm.

The overall performance of the LASSO-based PIHCP model, considering the AUC, Omnibus, Nagelkerke  $R^2$ , and HL test results, corresponded well with the expected values in Table 4. The AUC and NPV of the optimal model were 0.79 (95% CI, 0.70–0.88) and 0.84, respectively (the expected values in this study were HL  $\geq 0.05$ , scaled Brier score (SB-S)  $\geq 0.05$ ,  $R^2 \geq 0.05$ , Omnibus  $\leq 0.05$ , AUC  $\geq 0.75$ ). Finally, a significant correlation between PIHCP and outcome for the LASSO-based PIHCP model was observed in the HL goodness of fit test. Table 4 lists the performance of the PIHCP model including between one and five selected predictive factors. The five selected predictive factors system used for this study was the optimal number of risk factors.



**Table 3.** Multivariate logistic regression coefficients and odds ratios.

Predictive Factors	$\beta$	<i>p</i> -Value	Odds Ratio	95% CI
(n = 5)				
Immediately Endpoints of Laser (IEL)				
Erythema (0)		0.02		
Petechiae (1)	1.41	0.06	4.09	0.95–17.71
Erythema mild Petechiae (2)	2.30	<0.01	9.92	1.78–55.27
AHA Peels	0.38	0.02	1.46	1.05–2.03
FSPT				
Type III (0)		0.26		
Type IV (1)	0.46	0.56	1.59	0.33–7.65
Type V (2)	1.23	0.10	3.43	0.75–15.06
Acnes				
Yes (1)	1.32	0.06	3.75	0.94–15.02
Melasma				
Yes (1)	0.57	0.34	1.76	0.56–5.59
Constant ( $\beta_0$ )	−3.29	<0.01	0.04	

Abbreviations: FSPT: Fitzpatrick skin phototype; AHA:  $\alpha$ -hydroxy acid; CI: Confidence Interval; n: selected predictive risk factors.

**Table 4.** System performance evaluation.

Predictive Factors Selected	HL	SB-S	$R^2$	Omnibus	AUC
IEL,	1.00	0.06	0.08	0.06	0.62 (0.48–0.77)
IEL, AHA Peels	0.60	0.09	0.13	0.02	0.67 (0.53–0.81)
IEL, AHA Peels, FSPT	0.82	0.10	0.16	0.03	0.73 (0.60–0.85)
IEL, AHA Peels, FSPT, Acnes	0.44	0.12	0.18	0.03	0.75 (0.63–0.87)
IEL, AHA Peels, FSPT, Acnes, Melasma	0.29	0.11	0.20	0.02	0.79 (0.70–0.88)

Abbreviations: FSPT: Fitzpatrick skin phototype; IEL: Immediately Endpoints of Laser; AHA:  $\alpha$ -hydroxy acid; Nevus. AUC: Area under the receiver operating characteristic curve; HL: Hosmer–Lemeshow test; SB-S: Scaled Brier score; the first five predictive factors were IEL, AHA Peels, FSPT, Acnes, and Melasma.

#### 4. Discussion

PIH is a common skin complication in patients after treatment with lasers and other light sources [6]. As no objective prediction model is available at present, this side effect is predicted based on medical history. However, we found that PIH can be predicted in laser toning patients using the LASSO-based PIHCP model with cross-validation. The incidence of PIH in laser toning patients in this study was 16.8% (NPV = 84%). Similar reports by Sugawara et al. [2] and Chan et al. [21] showed that pigmented disorders can be easily controlled by laser toning therapy, but complications may occur. The incidence of rebound hyperpigmentation or hypopigmentation associated with laser toning was reported to range from 0% to 16.8% [2,3,5,21].

For the PIHCP model with the LASSO algorithm, the most important risk factors for PIHCP were IEL, AHA peel, FSPT, acne, and melasma. The AUC improved from 0.62 to 0.79 when the number of risk predictive factors used was increased from one (IEL) to five (AHA peel, FSPT, acne, and melasma; Table 4). An appropriate set of predictive factors can limit the risk of PIH in patients treated with Q-switched Nd-YAG laser toning. Risk prediction models for PIH could optimize current laser toning therapies and indicate which risk factors are the most important to limit the rate of complications. The incidence of PIH could be reduced if the risk factors are handled appropriately.

Among the predictive factors tested in our models, the most significant was IEL. The major negative outcome of laser treatment is early tissue reactions occurring immediately after laser treatment, which provide a reliable indication of tissue injury. Wanner et al. reported that IEL is an indicator of laser-tissue reaction and PIH is caused by inflammation [4,19]. Thus, the occurrence of immediate-onset laser–tissue reaction is a strong indicator of the possibility of PIH [4,19]. A similar report by Song et al.

showed increased epidermal pigmentation and expression of certain inflammatory cytokines after laser irradiation, suggesting that they may be responsible for induction of PIH [5]. We found that patients with IEL had a higher probability of petechiae. This result indicated inflammation and injury to the skin tissue, and therefore a greater likelihood of developing PIH.

The PIH risk was higher in patients receiving AHA peels than in those without AHA peels in this study. With application of AHA peels,  $\alpha$ -hydroxy acid may be dispersed within the basal layer melanin via epidermolysis [22]. Although AHA peels can be used to treat patients with PIH [22], they can also cause mild inflammation and injury to the skin, which can potentially exacerbate PIH [23]. The addition of laser toning can result in skin irritation, leading to PIH. To avoid irritation, care should be taken when using an AHA peel in combination with laser toning, which can cause PIH.

As the epidermal melanin content is high in Asian skin, adverse pigmentary effects are more likely to occur after laser treatment [1,24]. PIH increases pigmentation secondary to an acquired inflammatory process, which occurs more easily in FSPTs III and VI and can have a considerable effect on quality of life [25]. Therefore, skin color is a significant risk factor for PIH, with deeper skin color requiring more care. A study performed in Singapore indicated that Asians with darker skin are more likely to develop PIH than Asians with lighter skin, suggesting that the degree of pigmentation may have a stronger association with PIH than race [23].

With regard to acne as a risk factor, Abad-Casintahan et al. reported that PIH is a particularly common sequela to acne in darker skin types (Fitzpatrick phototypes III–VI) [23,25]. Acne-related PIH can be more problematic than the acne. Erica et al. reported that PIH may occur without obvious clinical inflammation in patients with mild to moderate acne [6]. Acne was an important predictive risk factor for PIH in this study. PIH may be worsened by laser toning in acne patients, but data are limited regarding this issue. Physicians should take this risk factor into consideration when treating patients with Nd-YAG laser toning.

With regard to melasma, FSPT and melasma facilitate melanin production. An increase in melanin can be induced by stronger laser treatment. Both Narumol et al. and Kim et al. reported that rebound PIH occurs frequently with laser toning for treatment of melasma and skin rejuvenation [6,26].

Our results are similar to those of Narumol et al., who suggested that the intensity of PIH is determined by the inherent skin color, inflammatory conditions, and melanocyte stability [6].

Although PIH is an important complication in patients undergoing multisession laser toning [6], in the present study, treatment frequency was the least important predictive factor in patients undergoing laser toning. As it involves downregulation of melanogenesis (resulting in decreased melanocyte function) [27], hypopigmentation may be a consequence of cumulative phototoxic damage to melanocytes and keratinocytes caused by laser therapies [2,21,28]. Frequent use of laser toning may result in increased formation of hypopigmented macules [2,21,29]. Patients undergoing multiple sessions of laser toning should be made aware of the potential complications [29].

This study had some limitations: the treatment modalities may have differed among countries and institutes, where differences in laser toning methods may be associated with variation in PIH severity. The study population was small. To promote adoption of the PIHCP model and reduce the uncertainties, longer-duration prospective studies including larger populations are required.

## 5. Conclusions

The predictive risk factor model described herein will be useful to further optimize laser toning treatment with respect to PIH. This LASSO-based PIHCP model indicates the most important risk factors for PIH (IEL, AHA peel, FSPT, acne, and melasma), which will aid in decision making regarding treatment, thus helping to reduce PIH as much as possible and in the optimization of current laser toning treatment protocols. The LASSO-based PIHCP model could be used to identify the risk factors for the incidence of PIH complications after laser toning. Our results show the five important risk factors selected by LASSO. The most important factor, IEL, was added to the prediction model when the AUC was 0.62. The prediction model was added one by one according to the importance of the



factors. The AUC gradually increased to 0.79 when all five factors were added. We found that when these five risk factors were simultaneously included in the prediction model, the model's prediction ability was the best.

**Author Contributions:** C.-H.L. (Chao-Hong Liu), C.-S.S., T.-L.H., Y.-J.H., J.-M.W., and T.-F.L. developed the research content based on the analysis and drafted the manuscript. C.-H.L. (Chih-Hsueh Lin), P.-J.C., S.-A.Y., C.-D.T., H.-F.L., and S.W.L. provided academic feedback on the study and revised the manuscript. T.-F.L. directed the research process and supervised the overall work. All authors read and approved the final manuscript.

**Acknowledgments:** We thank Jian-Zhi Pan, Zih-Xiang Su, and Yu-Ting Chen for the statistical technical support. This study was supported financially, in part, by grants from MOST-107-2221-E-992-014-MY2 and MOST-109-2623-E-992-006 -NU.

**Conflicts of Interest:** The authors declare no conflicts of interest. Part of this results was presented in an abstract form at the 6th Continental Congress of Dermatology.

**Ethical Statement:** Ethical Statement: Institutional Review Board (IRB) approval was obtained from the Kaohsiung Yuan's General Hospital IRB (approval number: 20161031-2B), and the requirement for informed consent was waived given the retrospective nature of the study.

## References

1. Li, J.Y.; Geddes, E.R.; Robinson, D.M.; Friedman, P.M. A review of melasma treatment focusing on laser and light devices. *Semin. Cutan. Med. Surg.* **2016**, *35*, 223–232. [[CrossRef](#)]
2. Sugawara, J.; Kou, S.; Kou, S.; Yasumura, K.; Satake, T.; Maegawa, J. Influence of the frequency of laser toning for melasma on occurrence of leukoderma and its early detection by ultraviolet imaging. *Lasers Surg. Med.* **2015**, *47*, 161–167. [[CrossRef](#)]
3. Wanner, M.; Sakamoto, F.H.; Avram, M.M.; Chan, H.H.; Alam, M.; Tannous, Z.; Anderson, R.R. Immediate skin responses to laser and light treatments: Therapeutic endpoints: How to obtain efficacy. *J. Am. Acad. Dermatol.* **2016**, *74*, 821–833. [[CrossRef](#)] [[PubMed](#)]
4. Wanner, M.; Sakamoto, F.H.; Avram, M.M.; Anderson, R.R. Immediate skin responses to laser and light treatments: Warning endpoints: How to avoid side effects. *J. Am. Acad. Dermatol.* **2016**, *74*, 807–819. [[CrossRef](#)] [[PubMed](#)]
5. Song, H.S.; Kang, H.Y. Time sequential changes of melanocytes and melanogenic factors in laser-induced postinflammatory hyperpigmentation: P6854. *J. Am. Acad. Dermatol.* **2013**, *68*, AB190.
6. Silpa-Archa, N.; Kohli, I.; Chaowattanapanit, S.; Lim, H.W.; Hamzavi, I. Postinflammatory hyperpigmentation: A comprehensive overview: Epidemiology, pathogenesis, clinical presentation, and noninvasive assessment technique. *J. Am. Acad. Dermatol.* **2017**, *77*, 591–605. [[CrossRef](#)] [[PubMed](#)]
7. Xu, C.-J.; van der Schaaf, A.; Schilstra, C.; Langendijk, J.A.; van't Veld, A.A. Impact of statistical learning methods on the predictive power of multivariate normal tissue complication probability models. *Int. J. Radiat. Oncol. Biol. Phys.* **2012**, *82*, e677–e684. [[CrossRef](#)]
8. Xu, C.-J.; van der Schaaf, A.; Van't Veld, A.A.; Langendijk, J.A.; Schilstra, C. Statistical validation of normal tissue complication probability models. *Int. J. Radiat. Oncol. Biol. Phys.* **2012**, *84*, e123–e129. [[CrossRef](#)]
9. Xu, J.; Yin, J. Kernel least absolute shrinkage and selection operator regression classifier for pattern classification. *IET Comput. Vis.* **2013**, *7*, 48–55. [[CrossRef](#)]
10. Lee, T.-F.; Liou, M.-H.; Huang, Y.-J.; Chao, P.-J.; Ting, H.-M.; Lee, H.-Y.; Fang, F.-M. LASSO NTCP predictors for the incidence of xerostomia in patients with head and neck squamous cell carcinoma and nasopharyngeal carcinoma. *Sci. Rep.* **2014**, *4*, 6217. [[CrossRef](#)]
11. Kong, C.; Zhu, X.-Z.; Lee, T.-F.; Feng, P.-B.; Xu, J.-H.; Qian, P.-D.; Zhang, L.-F.; He, X.; Huang, S.-F.; Zhang, Y.-Q. LASSO-based NTCP model for radiation-induced temporal lobe injury developing after intensity-modulated radiotherapy of nasopharyngeal carcinoma. *Sci. Rep.* **2016**, *6*, 1–8. [[CrossRef](#)] [[PubMed](#)]
12. Langendijk, J.A.; Doornaert, P.; Rietveld, D.H.; Verdonck-de Leeuw, I.M.; Leemans, C.R.; Slotman, B.J. A predictive model for swallowing dysfunction after curative radiotherapy in head and neck cancer. *Radiother. Oncol.* **2009**, *90*, 189–195. [[CrossRef](#)] [[PubMed](#)]

13. Lee, T.-F.; Chao, P.-J.; Ting, H.-M.; Chang, L.; Huang, Y.-J.; Wu, J.-M.; Wang, H.-Y.; Horng, M.-F.; Chang, C.-M.; Lan, J.-H. Using multivariate regression model with least absolute shrinkage and selection operator (LASSO) to predict the incidence of xerostomia after intensity-modulated radiotherapy for head and neck cancer. *PLoS ONE* **2014**, *9*, e89700. [[CrossRef](#)] [[PubMed](#)]
14. Lee, T.-F.; Fang, F.-M. Quantitative analysis of normal tissue effects in the clinic (QUANTEC) guideline validation using quality of life questionnaire datasets for parotid gland constraints to avoid causing xerostomia during head-and-neck radiotherapy. *Radiother. Oncol.* **2013**, *106*, 352–358. [[CrossRef](#)] [[PubMed](#)]
15. Tibshirani, R. Regression shrinkage and selection via the lasso. *J. R. Stat. Soc. Ser. B (Methodol.)* **1996**, *58*, 267–288. [[CrossRef](#)]
16. Hastie, T.; Tibshirani, R.; Friedman, J.; Franklin, J. The elements of statistical learning: Data mining, inference and prediction. *Math. Intell.* **2005**, *27*, 83–85.
17. Wattanakrai, P.; Mornchan, R.; Eimpunth, S. Low-fluence Q-switched neodymium-doped yttrium aluminum garnet (1,064 nm) laser for the treatment of facial melasma in Asians. *Dermatol. Surg.* **2010**, *36*, 76–87. [[CrossRef](#)]
18. Beetz, I.; Schilstra, C.; Burlage, F.R.; Koken, P.W.; Doornaert, P.; Bijl, H.P.; Chouvalova, O.; Leemans, C.R.; de Bock, G.H.; Christianen, M.E. Development of NTCP models for head and neck cancer patients treated with three-dimensional conformal radiotherapy for xerostomia and sticky saliva: The role of dosimetric and clinical factors. *Radiother. Oncol.* **2012**, *105*, 86–93. [[CrossRef](#)]
19. Beetz, I.; Schilstra, C.; van der Schaaf, A.; van den Heuvel, E.R.; Doornaert, P.; van Luijk, P.; Vissink, A.; van der Laan, B.F.; Leemans, C.R.; Bijl, H.P. NTCP models for patient-rated xerostomia and sticky saliva after treatment with intensity modulated radiotherapy for head and neck cancer: The role of dosimetric and clinical factors. *Radiother. Oncol.* **2012**, *105*, 101–106. [[CrossRef](#)]
20. Chan, N.P.; Ho, S.G.; Shek, S.Y.; Yeung, C.K.; Chan, H.H. A case series of facial depigmentation associated with low fluence Q-switched 1,064 nm Nd: YAG laser for skin rejuvenation and melasma. *Lasers Surg. Med.* **2010**, *42*, 712–719. [[CrossRef](#)]
21. Sim, J.H.; Park, Y.L.; Lee, J.S.; Lee, S.Y.; Choi, W.B.; Kim, H.J.; Lee, J.H. Treatment of melasma by low-fluence 1064 nm Q-switched Nd: YAG laser. *J. Dermatol. Treat.* **2014**, *25*, 212–217. [[CrossRef](#)] [[PubMed](#)]
22. Rossi, A.M.; Perez, M.I. Treatment of hyperpigmentation. *Facial Plast. Surg. Clin.* **2011**, *19*, 313–324. [[CrossRef](#)] [[PubMed](#)]
23. Davis, E.C.; Callender, V.D. Postinflammatory hyperpigmentation: A review of the epidemiology, clinical features, and treatment options in skin of color. *J. Clin. Aesthetic Dermatol.* **2010**, *3*, 20.
24. Hirsch, R.; Stier, M. Complications and their management in cosmetic dermatology. *Dermatol. Clin.* **2009**, *27*, 507–520. [[CrossRef](#)] [[PubMed](#)]
25. Abad-Casintahan, F.; Chow, S.K.W.; Goh, C.L.; Kubba, R.; Hayashi, N.; Noppakun, N.; See, J.; Suh, D.H.; Xiang, L.H.F.; Kang, S. Frequency and characteristics of acne-related post-inflammatory hyperpigmentation. *J. Dermatol.* **2016**, *43*, 826–828. [[CrossRef](#)]
26. Kim, B.W.; Lee, M.H.; Chang, S.E.; Yun, W.J.; Won, C.H.; Lee, M.W.; Choi, J.H.; Moon, K.C. Clinical efficacy of the dual-pulsed Q-switched neodymium: Yttrium-aluminum-garnet laser: Comparison with conservative mode. *J. Cosmet. Laser Ther.* **2013**, *15*, 340–341. [[CrossRef](#)]
27. Kim, J.E.; Chang, S.; Yeo, U.; Haw, S.; Kim, I.H. Histopathological study of the treatment of melasma lesions using a low-fluence Q-switched 1064-nm neodymium: Yttrium-aluminum-garnet laser. *Clin. Exp. Dermatol. Clin. Dermatol.* **2013**, *38*, 167–171. [[CrossRef](#)]
28. Kim, M.; Kim, J.; Cho, S. Punctate leucoderma after melasma treatment using 1064-nm Q-switched Nd: YAG laser with low pulse energy. *J. Eur. Acad. Dermatol. Venereol.* **2009**, *23*, 960–962. [[CrossRef](#)]
29. Wong, Y.; Lee, S.S.J.; Goh, C.L. Hypopigmentation induced by frequent low-fluence, large-spot-size QS Nd: YAG laser treatments. *Ann. Dermatol.* **2015**, *27*, 751–755. [[CrossRef](#)]

