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Treatment outcome and prognostic factors of tonsillectomy for palmoplantar pustulosis and pustulotic arthro－osteitis: A retrospective subjective and objective quantitative analysis of 138 patients

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Title page

Full title: Treatment outcome and prognostic factors of tonsillectomy for palmoplantar pustulosis and pustulotic arthro-osteitis: A retrospective subjective and objective quantitative analysis of 138 patients.

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Running title: Tonsillectomy for PPP and PAO

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ABSTRACT

Pustulosis palmaris et plantaris (PPP) and pustulotic arthro-osteitis (PAO) are tonsil-related diseases. Treatment outcome of tonsillectomy and prognostic factors influencing the outcome have not been analyzed quantitatively. We evaluated those using the PPP area and severity index (PPPASI). At 1 month, 3 months, 6 months, 12 months, 24 months, and >24 months post-tonsillectomy, 20 (31%) patients, 34 (48%) patients, 70 (60%) patients, 57 (80%) patients, 36 (95%) patients, and 23 (96%) patients realized ≥80% improvement of PPP skin lesions, respectively, and 8 (17%) patients, 23 (36%) patients, 30 (50%) patients, 38 (79%) patients, 12 (100%) patients, and 4 (100%) patients showed ≥80% improvement of PPPASI (i.e., PPPASI% ≥80%), respectively. At 1 month, 3 months, 6 months, 12 months, and >12 months post-tonsillectomy, 19 (73%) patients, 21 (66%) patients, 27 (73%) patients, 19 (79%) patients, and 15 (83%) patients realized a disappearance of PAO-induced arthralgia, respectively. Kaplan–Meier analysis of 80 patients with PPP revealed that, at 12 months and 24 months post-tonsillectomy, lesions disappeared (i.e., PPPASI = 0) in 38% and 66% of patients, respectively, and lesions improved ≥80% (i.e., PPPASI% ≥80%) in 71% and 95% of patients, respectively. The log-rank test and univariate and multivariate analyses showed that smoking cessation post-tonsillectomy and PAO were significant predictive factors for the early disappearance of skin lesions. This report is the first demonstrating objective evidence of the great efficacy of tonsillectomy to improve PPP skin lesions. Even post-tonsillectomy, smoking inhibited the early disappearance of the lesions.

INTRODUCTION

Palmoplantar pustulosis (PPP) is characterized by symmetric, erythematous, scaly plaques with numerous, sterile, nonbacterial, pinpoint pustules that are restricted to the palms and soles. Palmoplantar pustulosis is often classified as a localized form of pustular psoriasis, [1] however, the definition or pathogenesis of PPP and pustular psoriasis has been still argumentative. Palmoplantar pustulosis occurs in approximately 0.05% of the population and occurs more frequently in women 30–60 years old.[2] Exacerbation of PPP occurs after upper respiratory infections, particularly acute tonsillitis[3, 4]; therefore, it may be a typical tonsil-related disease.

With regard to the clinical outcome of tonsillectomy to treat skin lesions of patients with PPP, Andrews et al.[3] first reported that nine of 24 Caucasian patients with PPP were entirely cured of PPP after tonsillectomy. After the Andrews study, research demonstrating the effectiveness of tonsillectomy for PPP has primarily come from Japan. In 1977, Ono et al.[5] reported that 73 tonsillectomized patients had significantly better improvement than 83 patients who received other treatment methods (84% vs. 39%, $p<0.01$). In another study, Ono et al.[6] uninterruptedly reported that, among 124 patients with PPP enrolled by questionnaire survey, 59.2% and 71.8% of the patients were respectively cured at 1 year and 2 years after tonsillectomy, based on Kaplan–Meier analysis; these percentages were significantly higher than those of patients treated by other methods (e.g., corticosteroid therapy, psoralen and ultraviolet A radiation therapy). In 1996, Kataura et al.[4] examined 289 patients with PPP who underwent tonsillectomy, and showed that 255 (88.1%) patients had >50% improvement in the skin lesion after tonsillectomy, based on self-assessment. In 2004, Yokoyama et al.,[7] based on their questionnaire investigation, reported 89% (55/62) of patients with PPP showed more marked improvement of PPP skin lesion after tonsillectomy. We previously conducted a prospective case series of 116 patients with PPP who underwent tonsillectomy, and found that 94% (109/116) of patients reported that their skin lesions improved after tonsillectomy.[8] These results suggest that tonsillectomy is very effective

in alleviating PPP skin lesions. However, nearly all reports employed subjective evaluations of PPP skin lesions, based on patients' self-assessment.

Bhushan, et al [9] proposed using the Palmoplantar Pustulosis Area and Severity Index (PPPASI) as an objective evaluation method for quantifying PPP skin lesions. This method makes it possible to objectively evaluate the skin condition of patients with PPP after tonsillectomy.

Sternocostoclavicular hyperosteosis (SCCH) is hyperostosis that primarily affects the intrasternocostoclavicular joints, and induces painful swelling of the affected joints.[10] It frequently accompanies PPP, a combination that is called pustulotic arthro-osteitis (PAO).[11] Moreover, the combination of PPP and PAO has been proposed as a syndromic disorder comprising synovitis, acne, PPP, hyperostosis, and ostitis (SAPHO).[12] In other studies, [13, 14] Kataura reported that 52% (46/89) of patients with SCCH or PAO experienced that disappearance of or a remarkable improvement in joint pain for longer than 3 months during the observation period. Therefore, like PPP, PAO is also considered a typical tonsil-related disease.[4]

The treatment outcome and prognostic factors of the tonsil-related diseases PPP have not been analyzed quantitatively. Therefore, in the current study, we evaluated skin lesions in patients with PPP before and after tonsillectomy by using a conventional subjective method (i.e., patient self-assessment) and by using an objective measure, the Palmoplantar pustulosis Area and Severity Index. Moreover, we performed Kaplan–Meier analysis using PPPASI values, and attempted to determine predictive factors for the improvements in skin lesions, based on the log-rank test and univariate and multivariate analyses.

MATERIALS AND METHODS

Patients' characteristics

One hundred thirty-eight patients with PPP, who underwent tonsillectomy in the Department of Otolaryngology-Head and Neck Surgery at Asahikawa Medical

University (Asahikawa, Japan) during 1998–2016, were enrolled in this study. All patients were diagnosed as having PPP and referred to our department by dermatologists, who wanted the patients to undergo tonsillectomy because the PPP skin lesions were refractory to conservative treatment. Clinical information was obtained retrospectively from hospital charts or by direct interview. Table 1 lists the clinical characteristics in each study: age, sex, period of having the disease before treatment, presence of PAO, deterioration of PPP skin lesion with the upper respiratory infection, smoking status, tonsillar hypertrophy (i.e., modified Mackenzie classification of ≥II), high serum antistreptolysin O (ASO) level, transient deterioration of the skin lesion after tonsillectomy, quitting smoking within 1 month after tonsillectomy, and the observation period after tonsillectomy. The diagnosis of PAO is based on painful swelling in the sternoclavicular region where bone scintigraphy showed typical uptake.[11] Modified Mackenzie classification was subjected to Selma's report.[15] Briefly, tonsils inside the tonsillar fossa lateral posterior pillars was classified in grade I, and tonsils outside the pillars was classified in grade ≥II.

This study was approved by the medical ethics committee of Asahikawa Medical University of Medical Science (approval no. 224-5). We obtained written informed consents from all participants of this study.

Patients' self- assessment of PPP skin lesions after tonsillectomy

The Skin Severity Score (SSS) was used to evaluate the severity of palmar and plantar lesions in each patient, as described previously.[4, 16] In brief, the 138 patients subjectively evaluated their skin conditions after tonsillectomy on SSS value of 1 to 10; the condition before tonsillectomy was defined as SSS 10. If the patients realized that PPP skin lesions had completely disappeared after tonsillectomy, they were expected to answer that the SSS was 0. In 85 of 138 patients, SSS in palms was separately evaluated from SSS in soles. In those cases, total SSS was obtained by average of SSS in palms and soles.

Patients' self- assessment of PAO-induced arthralgia after tonsillectomy.

The Pain Severity Score (PSS) was used to evaluate the severity of arthralgia caused by PAO. Fifty patients with PAO subjectively evaluated their pain after tonsillectomy on a scale of 1 to 10; the PSS for pain before tonsillectomy was defined as PSS 10. If the patients realized that their pain had completely disappeared after tonsillectomy, they were expected to answer that PSS was 0.

The PPPASI scoring of PPP skin lesions before and after tonsillectomy

Skin lesions in 80 of 138 patients were evaluated by PPPASI scoring proposed by Bhushan, et al.[9] This index is used widely to assess the severity of chronic plaque psoriasis.[17] In brief, erythema (E), pustules (P), and desquamation (D) were evaluated on a scale of 0 to 4, whereas the area was evaluated on a scale of 0 to 6. The following formula was used for quantification: score = (E + P + D) × area × 0.2 (right palm) + (E + P + D) × area × 0.2 (left palm) + (E + P + D) × area × 0.3 (right sole) + (E + P + D) × area × 0.3 (left sole).

The PPPASI can vary from 0 (i.e., absence of disease) to 72 (i.e., most severe palmoplantar psoriasis possible). In addition, the improvement rate of PPPASI (PPPASI%) was calculated by dividing the decrement in the PPPASI through tonsillectomy by the PPPASI value before tonsillectomy.

Kaplan–Meier analysis in the improvement of PPP skin lesions and PAO arthralgia

Kaplan–Meier analyses were used for the time-to-event analyses. The primary end point was the disappearance of a skin lesion (i.e., PPPASI = 0 or SSS = 0) or the disappearance of arthralgia (PSS = 0). The secondary end point was an improvement of ≥80% in the lesion (i.e., PPPASI% ≥ 80%, SSS ≤ 2, or PSS ≤ 2). Patients whose skin lesions or arthralgia worsened after initially disappearing or improving ≥80% were

considered as censored case.

Treatment outcome, based on variable clinical factors associated with an improvement in PPP skin lesions

Eighty patients with PPP who were scored by using the PPPASI were divided into two groups, based on each clinical factor as follows: patients' age (≥53 or <53 years; median age, 53 years), sex, presence or absence of comorbid PAO, period of having the disease before treatment (≥2 or <2 years; median period, 2 years), deterioration in the skin lesion with an the upper respiratory infection (yes or no**)**, smoker (yes or no**)**, tonsillar hypertrophy level (modified Mackenzie classification I or ≥II), serum level of ASO (high or normal**)**, PPPASI value before tonsillectomy (≥7.8 or <7.8; median value, 7.8), transient deterioration in the PPP skin lesion after tonsillectomy (presence or absence**)**, or smoking cessation after tonsillectomy within 1 month after tonsillectomy (yes or no).

The two groups were compared by using log-rank test and univariate analysis. Moreover, the clinical factors with p <0.3 under univariate analysis were extracted for multivariate analysis.

Statistics

Two-group time dependent comparisons were tested appropriately using the Wilcoxon signed-rank test. To determine the associated factors, clinical variables selected by univariate analysis were entered in a multivariable logistic regression model. Statistical analyses were performed using JMP 11® (SAS Institute Inc., Cary, NC). Statistical tests were based on a level of significance level of $P < 0.05$.

RESULTS

Skin Severity Score (SSS) after tonsillectomy

Postoperative changes in the SSS over time are shown in Figure 1a and Table 2. At 1 months, 3 months, 6 months, 12 months, 24 months, >24 months, and last visit after

tonsillectomy, the median and 25–75 percentile of the SSS were respectively 4 and 2–6; 3 and 1–5; 2 and 0–4; 1 and 0–2; 0 and 0–1; 0 and 0–1; and 1and 0–2. The SSS decreased significantly over time within 24 months after tonsillectomy. At 1 month, 3 months, 6 months, 12 months, 24 months, >24 months, and last visit after tonsillectomy, PPP skin lesions disappeared (i.e., SSS = 0) in 3 (5%) patients, 12 (17%) patients, 30 (26%) patients, 28 (44%) patients, 21 (55%) patients, 16 (67%) patients, and 60 (43%) patients, respectively. In addition, 20 (31%) patients, 34 (48%) patients, 70 (60%) patients, 57 (89%) patients, 36 (94%) patients, 23 (95%) patients, and 106 (77%) patients had ≥80% improvement in the lesion (i.e., SSS ≤2) at 1 month, 3 months, 6 months, 12 months, 24 months, >24 months, and last visit after tonsillectomy, respectively.

Kaplan–Meier analysis revealed that, at 12 months and 24 months after tonsillectomy, the PPP lesion disappeared (i.e., SSS = 0) in 38% and 66% of patients respectively (Figure 1b), and improved ≥80% (i.e., SSS ≤2) in 71% and 95% of patients, respectively (Figure 1c).

SSS of palms or soles after tonsillectomy

Postoperative changes in the SSS of palms over time are shown in Figure 2a and Table 3. At 1 months, 3 months, 6 months, 12 months, 24 months, >24 months, and last visit after tonsillectomy, the median and 25–75 percentile of the SSS were respectively 3 and 2–6; 2 and 0–5; 1 and 0–3.5; 0 and 0–2; 0 and 0–0; 0 and 0–0; and 0 and 0–2. The SSS decreased significantly over time within 12 months after tonsillectomy.

Postoperative changes in the SSS of soles are shown in Figure 2b and Table 3. At 1 months, 3 months, 6 months, 12 months, 24 months, >24 months, and last visit after tonsillectomy, the median and 25–75 percentile of the SSS were respectively 4 and 1–6; 2 and 1–5; 2 and 0–4; 1 and 0–3; 0 and 0–0.5; 0 and 0–1; and 0 and 0–3. The SSS significantly decreased between before tonsillectomy and one month after tonsillectomy,

6 months and 12 months after tonsillectomy, or 12 months and 24 months after tonsillectomy.

Kaplan–Meier analysis revealed that the PPP lesion of palms and that of soles disappeared (i.e., SSS of palms or soles = 0) in 51% and 38% of patients at 12 months after tonsillectomy, respectively (Figure 2c), and improved ≥80% (i.e., SSS of palms or soles ≤2) in 87% and 71% of patients, respectively (Figure 2d). According to Kaplan–Meier curves, the rate of disappearance or ≥80% improvement in PPP lesion of palms seemed to be higher than that of soles at each time point, however, the difference was not statistically significant (disappearance p=0.08, ≥80% improvement p=0.11).

A pain severity score (PSS) after tonsillectomy

Postoperative change in the PSS is shown in Figure 3a and Table 4. At 1 month, 3 months, 6 months, 12 months, >12 months, and last visit after tonsillectomy, the median and 25–75 percentile of the PSS were 0 and 0–3.5; 0 and 0–3.75; 0 and 0–1; 0 and 0–0; 0 and 0–0; and 0 and 0–1, respectively. The PSS was significantly decreased in each of these observation periods, compared to before tonsillectomy. At 1 month, 3 months, 6 months, 12 months, >12 months, and last visit after tonsillectomy, PAO arthralgia disappeared (i.e., PSS = 0) in 19 (73%) patients, 21 (66%) patients, 27 (73%) patients, 19 (79%) patients, 15 (83%) patients, and 36 (72%) patients, respectively. In addition, at 1 month, 3 months, 6 months, 12 months, >12 months, and last visit after tonsillectomy, PAO arthralgia improved ≥80% (i.e., PSS ≤2) in 19 (73%) patients, 22 (69%) patients, 30 (82%) patients, 21 (87%) patients, 18 (100%), and 43 (86%) patients, respectively.

Kaplan–Meier analysis revealed that, at 6 months and 12 months after tonsillectomy, PAO arthralgia disappeared (i.e., PSS = 0) in 68% and 78% of patients respectively (Figure 3b), and improved ≥80% (i.e., PSS ≤ 2) in 75% and 87% of the patients, respectively (Figure 3c).

PPPASI before and after tonsillectomy

Changes in the PPPASI before and after tonsillectomy are shown in Figure 4a and Table 5. At first visit before tonsillectomy, 1 month, 3 months, 6 months, 12 months, 24 months, >24 months, and last visit after tonsillectomy, the median and the 25–75 percentile of the PPPASI were 7.8 and 2.8–14.1; 2.7 and 1.025–7.5; 1.8 and 0.6–5.75; 1.2 and 0–4.8; 0 and 0–1.2; 0 and 0–0; 0 and 0–0; and 0 and 0–1.4, respectively. The PPPASI significantly decreased over time within 12 months after tonsillectomy.

Changes in the PPPASI% after tonsillectomy are shown in Figure 4b and Table 5. At 1 month, 3 months, 6 months, 12 months, 24 months, >24 months, and last visit after tonsillectomy, the median and 25–75 percentile of the PPPASI% were 40.6% and 18.6%–66.7%; 71.5% and 44.1%–91.3%; 78.3% and 55.2%–100%; 100% and 83.6%–100%; 100% and 100%–100%; 100% and 100%–100% and 100% and 76%–100%, respectively. The PPPASI% significantly increased over time within 24 months after tonsillectomy.

At 1 month, 3 months, 6 months, 12 months, 24 months, >24 months, and last visit after tonsillectomy, the PPP skin lesion disappeared (i.e., PPPASI = 0) in 3 (6%) patients, 13 (20%) patients, 20 (33%) patients, 26 (54%) patients, 10 (83%) patients, 4 (100%) patients, and 42 (53%) patients, respectively. In addition, at 1 month, 3 months, 6 months, 12 months, 24 months, >24 months, and last visit after tonsillectomy, the PPPASI improved ≥80% (i.e., PPPASI% ≥80%) in 8 (17%) patients, 23 (36%) patients, 30 (50%) patients, 38 (79%) patients, 12 (100%) patients, 4 (100%) patients, and 57 (71%) patients, respectively.

Kaplan–Meier analysis revealed that, at 12 months and 24 months after tonsillectomy, 44% and 78% of patients, respectively, had 100% improvement in the PPPASI (Figure 4c), and that 70% and 95% of patients, respectively, had ≥80% improvement in the PPPASI (Figure 4d)

Clinical factors correlated with the PPPASI before tonsillectomy or the presence of PAO

Clinical factors correlated with the PPPASI before tonsillectomy or with the presence PAO are shown in Table 6. The PPPASI value before tonsillectomy was significantly higher in patients who experienced an exacerbation in their PPP skin lesions with an upper respiratory infection, who smoked, or who failed to quit smoking after tonsillectomy, compared to patients who had not experienced an exacerbation, who did not smoke, or who successfully quit smoking. Moreover, the incidence of PAO in patients who had PPP for more than 3 years before tonsillectomy was significantly higher, compared to its incidence in patients with PPP less than 3 years.

Correlation between SSS, PSS, and PPPASI%

The correlation between SSS, PSS, and PPPASI% are shown in Figure 5. After tonsillectomy, there was significant negative correlation between the SSS and PPPASI% at 1 month, 3 months, 6 months (Figure 5a), and at 12 months and the last visit (Figure 5b). However, there was no significant correlation between the PSS and PPPASI%, or between the PSS and the SSS at any observation period, including last visit after tonsillectomy (Figures 5c and d).

Clinical factors contributing to the improvement in the PPP skin lesion after tonsillectomy

The results of log-rank tests are summarized in Table 7. Successfully quitting smoking after tonsillectomy and a PPPASI value < 7.8 were the clinical factors that significantly predicted the disappearance of PPP skin lesions (i.e., PPPASI = 0). Moreover, the presence of PAO was a factor that significantly predicted a ≥80% improvement in the PPP skin lesion (i.e., PPPASI% ≥ 80%).

The results of univariate and multivariate analysis, based on Cox proportional-hazards model are summarized in Table 8. Univariate analysis also revealed that quitting smoking, a PPPASI value ≥ 7.8, and the presence of PAO were significant predictive factors impacting the postoperative course of PPP skin lesion.

Moreover, multivariate analysis revealed that quitting smoking was an independent predictor for the disappearance of PPP skin lesion, and the presence of PAO was a predictor for the disappearance of and a greater than 80% improvement in a PPP skin lesion.

DISCUSSION

In this study, around 90% of patients with PPP experienced an improvement of their skin lesion after tonsillectomy at 12 months after tonsillectomy, based on objective and subjective evaluation methods. This report is the first demonstrating objective evidence of the great efficacy of tonsillectomy for improving PPP skin lesions, as analyzed using PPPASI. With some conservative treatments such as local steroid and psoralen and ultraviolet A, research also shows that >60% of patients have an improvement in their skin; however, a relapse cannot be avoided after stopping the treatment and a complete cure cannot be achieved.[7] With Regard to a change in PPP skin lesion after tonsillectomy over time, Kaplan–Meier analysis in the current study revealed that the PPP skin lesion disappeared at 12 months and 24 months after tonsillectomy in 44% and 87% of patients, respectively. Ono et al.[6] have also reported that 59% and 72% of the patients were cured at the same time points, based on Kaplan–Meier analysis. Therefore, to determine the efficacy of tonsillectomy for PPP skin lesions, clinicians should follow patients at least 24 months after tonsillectomy.

Kataura et al. [13, 14] reported that 90 (31%) of 289 tonsillectomized patients with PPP also had PAO, and that arthralgia caused by PAO disappeared in 46 (52%) patients for longer than 3 months during the observation period. In this study, we similarly found that 50 (36%) of 138 tonsillectomized patients with PPP had PAO, and the arthralgia had disappeared 3 months after tonsillectomy in 21 (66%) of 32 patients. No report exists concerning clinical factors in patients with PPP that has demonstrated its strong association with PAO. This study is the first showing a positive correlation between the period from the onset of PPP to tonsillectomy and the presence of PAO.

This result suggests that early treatment intervention for patients with PPP may prevent the development of PAO. Kaplan–Meier analysis revealed that, at 6 months and 12 months after tonsillectomy, 68% and 78% of patients, respectively, showed the disappearance of PAO arthralgia. The percentage reached a plateau at 12 months after tonsillectomy. Therefore, to determine the efficacy of tonsillectomy for PAO arthralgia, 12 months are sufficient to follow up patients after tonsillectomy. This effect was seen earlier than that of the PPP skin lesions after tonsillectomy. A reason may be that evaluation indicator of PAO was arthritis pain. If we used uptake of bone scintigraphy in sternoclavicular region as evaluation indicator, the results might be different. In fact, we experienced a patient with PAO who underwent a routine bone scintigraphy after tonsillectomy. It spent 10 years after tonsillectomy to decrease the uptake of region.

We found two independent clinical factors that predicted a favorable outcome for PPP skin lesions after tonsillectomy: presence of PAO and quitting smoking after tonsillectomy. Tonsil-related factor such as tonsillar hypertrophy and deterioration of PPP skin lesions with upper respiratory infection were not significantly related to disappearance or improvement of PPP skin lesions after tonsillectomy. We cannot resolve why the presence of PAO indicates a favorable outcome for PPP skin lesion. Based on our basic research, we speculate that a number of activated tonsillar T-cells,[16] which express several receptors such as cutaneous lymphocyte-associated antigen,[18] chemokine receptor 6,[19] and beta-1 integrin,[20] is increased by a hyper-immune response against alpha-streptococci (i.e., tonsil indigenous bacteria). These tonsillar T-cells migrate into PPP skin lesions, which express their ligands. Yayama, et al.[21] have shown the infiltration of several types of inflammatory cells including T-cells and sterile pustules in PAO lesions. The pathogenesis of PAO is less well understood than that of PPP; however, tonsillar T-cells may migrate into the affected joints and produce sterile pustule, as well as a PPP skin lesion.

It is very interesting that quitting smoking after tonsillectomy was a predictive factor. It has been reported that smokers have a 74-fold higher risk for PPP, compared to

non-smokers, and that skin lesions are more severe in smoking patients with PPP than in non-smoking patients.[22] We also showed that PPPASI was significantly higher in smoking patients than that in non-smoking patients. The cessation of smoking has been shown to improve PPP skin lesions in the previous resport.[23] Therefore, the effect of quitting smoking that we noted may have occurred, regardless of tonsillectomy. However, anesthesiologist generally recommend that patients who are to undergo intratracheal intubation under general anesthesia stop smoking before operation. The advent of surgery must be an alluring opportunity for patients to stop smoking. In fact, 27 (49%) out of 55 patients who smoked were able to stop smoking after tonsillectomy in this study. This smoking cessation rate is comparable with that of nicotine replacement therapy.[24] To increase the improvement rate of PPP skin lesion after tonsillectomy, clinicians should stress quitting smoking after tonsillectomy.

The development of a method to establish a diagnosis of tonsil-related disease is much expected. However, we have not found any clinical parameters that are suitable for the diagnosis. Another potential diagnostic method is the use of the tonsillar provocation test, which Nosaka et al [25] propounded in 1977. Changes in the body temperature, white blood cell count, and erythrocyte sedimentation rate have been examined, based on the conventional criteria for the provocation tests. However, patients who have negative results on these tests, based on the criteria, often improve after tonsillectomy.[26] Moreover, Kataura [27] showed that the tonsillar provocation test was positive in only 41.7% of patients with PPP. This percentage is substantially lower than that of the patients whose PPP skin lesion improved after tonsillectomy; therefore, the existing criteria may produce many false-negative results. Thus, the diagnostic utility of tonsillar provocation tests for PPP has not been fully established. As a consequence, we have not introduced using the test diagnostically for patients with PPP. After all, there is no method of diagnosing tonsil-related disease. Because of high efficacy of tonsillectomy in improving the skin lesions and arthralgia, clinicians should at least present tonsillectomy as treatment options to PPP and PAO patients who do not

show improvement with conventional treatment. In fact, we recommend tonsillectomy to most PPP patients who are referred by a dermatologist.

In summary, we showed the great efficacy of tonsillectomy for improving PPP skin lesion and PAO-induced pain, based on subjective self-assessment and on an objective method (i.e., the PPPASI). Moreover, quitting smoking and the presence of PAO were the significant factors that indicated disappearance of a skin lesion and an improvement ≥80% in the skin lesion, respectively. Otolaryngologists, dermatologists, and other doctors should share these findings and provide the best treatment for a patient suffering from PPP and PAO.

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CONFLICT OF INTEREST

The authors declare no conflict of interest relating to this publication.

REFERENCES

1. Asumalahti K, Ameen M, Suomela S, et al. Genetic analysis of PSORS1 distinguishes guttate psoriasis and palmoplantar pustulosis. *J Invest Dermatol* 2003; **120**: 627–632.
2. Hellgren L, Mobacken H. Pustulosis palmaris et plantaris. Prevalence, clinical observations and prognosis. *Acta Dermat Vener (Stockh)* 1971; **51**: 284–288.
3. Andrews GC, Machacek GF. Pustular bacterids of the hand and feet. *Arch Derm Syphilol* 1935; **32**: 837–847.
4. Kataura A, Tsubota H. Clinical analyses of focus tonsil and related diseases in Japan. *Acta Otolaryngol Suppl* 1996; **523**: 161–164.
5. Ono T. Evaluation of tonsillectomy as a treatment for pustulosis palmaris et plantaris. *J Dermatol*1977; **4**: 163–172.
6. Ono T, Jono M, Kito M, et al. Evaluation of tonsillectomy as a treatment for pustulosis palmaris et plantaris. *Acta Otolaryngol Suppl* 1983; **401**: 12–16.
7. Yokoyama M, Hashigucci K, Yamasaki Y. Effect of tonsillectomy in patients with pustulosis palmaris et plantaris. *Acta Otolaryngol* 2004; **124**: 1109–1110.
8. Takahara M. Clinical outcome of tonsillectomy for palmoplantar pustulosis and etiological relationship between palmoplantar pustulosis and tonsils. *Adv Otorhinolaryngol* 2011; **72**: 86–88.
9. Bhushan M, Burden AD, McElhone K, James R, Vanhoutte FP, Griffiths CE. Oral liarozole in the treatment of palmoplantar pustular psoriasis: a randomized, double-blind, placebo-controlled study. *Br J Dermatol* 2001; **145**: 546–553.
10. Kohler H, Uehlinger E, Kutzner J, West TB. Sternocostoclavicular hyperostosis: painful swelling of the sternum, clavicles, and upper ribs. Report of two new cases. *Ann Intern Med* 1977; **87**: 192–197.
11. Sonozaki H, Mitsui H, Miyanaga Y, et al. Clinical features of 53 cases with pustulotic arthro-osteitis. *Ann Rheum Dis* 1981; **40**: 547–53.
12. Chamot AM, Benhamou CL, Kahn MF, Beraneck L, Kaplan G, Prost A.

[Acne-pustulosis-hyperostosis-osteitis syndrome. Results of a national survey. 85 cases]. *Rev Rhum Mal Osteoartic* 1987; **54**: 187–96. In French.

13. Tsubota H, Kataura A, Kukuminato Y, et al. [Efficacy of tonsillectomy for improving skin lesions of pustulosis palmaris et plantaris—evaluation of 289 cases at the Department of Otolaryngology of Sapporo Medical University]. *Nihon Jibiinkoka Gakkai Kaiho* 1997; **97**: 1621–1630. In Japanese.

14. Ohguro S, Kataura A, Kukuminato Y, et al. [Tonsillectomy and osteoarthritic disease]. *Nihon Jibiinkoka Gakkai Kaiho* 1994; **97**: 1601–1607. IN Japanese.

15. Selma K, Hikmet F, Sadik A, Evaluation of upper airway in obstructive sleep apnea-hypopnea syndrome and habitual snorers. *Bratisl Lek Listy* 2009; **110**: 486-489.

16. Takahara M, Kishibe K, Nozawa H, Harabuchi Y. Increase of activated T-cells and up-regulation of Smad7 without elevation of TGF-beta expression in tonsils from patients with pustulosis palmaris et plantaris. *Clin Immunol* 2005; **115**: 192–199.

17. Fredriksson T, Pettersson U. Severe psoriasis--oral therapy with a new retinoid. *Dermatologica* 1978; **157**: 238–244.

18. Nozawa H, Kishibe K, Takahara M, Harabuchi Y. Expression of cutaneous lymphocyte-associated antigen (CLA) in tonsillar T-cells and its induction by in vitro stimulation with alpha-streptococci in patients with pustulosis palmaris et plantaris (PPP). *Clin Immunol* 2005; **116**: 42–53.

19. Yoshizaki T, Bandoh N, Ueda S, et al. Up-regulation of CC chemokine receptor 6 on tonsillar T cells and its induction by in vitro stimulation with alpha-streptococci in patients with pustulosis palmaris et plantaris. *Clin Exp Immunol* 2009; **157**: 71–82.

20. Ueda S, Takahara M, Tohtani T, Yoshizaki T, Kishibe K, Harabuchi Y. Up-regulation of ß1 integrin on tonsillar T cells and its induction by in vitro stimulation with alpha-streptococci in patients with pustulosis palmaris et

plantaris. *J Clin Immunol* 2010; **30**: 861–871.

21. Yayama T, Uchida K, Kobayashi S, Sato R, Baba H. Clinical and histological features of pustulotic arthro-osteitis: experience of 17 cases. *Japanese Journal of Rheumatism and Joint Surgery* 2005; **24**: 111–116.

22. Hagforsen E. The cutaneous non-neuronal cholinergic system and smoking related dermatoses: studies of the psoriasis variant palmoplantar pustulosis. *Life Sci* 2007; **80**(24-25): 2227–2234.

23. Michaelsson G, Gustafsson K, Hagforsen E. The psoriasis variant palmoplantar pustulosis can be improved after cessation of smoking. *J Am Acad Dermatol* 2006; **54**: 737–738.

24. Stead LF, Perera R, Bullen C, Mant D, Hartmann-Boyce J, Cahill K, et al. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev* 2012; **11**: CD000146.

25. Nosaka Y. Fundamental and Clinical Problems in Tonsil. Tokyo, Japan: Nihon Iji Shinpo Publications 1977. 285–287.

26. Shiraishi S, Tomoda K, Matsumoto A, Kyomoto R, Yamashita T. Investigation of the local provocation test to PPP and IgA nephritis. *Acta Otolaryngol Suppl Stockh* 1996; **523**: 178–181.

27. Kataura A, Shido F, Masuda Y, et al. Evaluation of the provocation test of tonsils: a report from the Committee for the standardization of diagnostic criteria for tonsillar focal infections. *Stomato-pharyngology* 1997; **9**: 213–221.

FIGURE LEGENDS

Figure 1. The Skin Severity Score (SSS) after tonsillectomy. (a) The 25%–75% percentile range and median value of the SSS at each time point. (b) Kaplan–Meier curves of the time-dependent percentage change in a patient whose skin lesion disappeared (i.e., SSS = 0) after tonsillectomy. (c) Kaplan–Meier curves of the time-dependent percentage change in a patient with ≥80% improvement (i.e., SSS ≤2) in the skin lesion post-tonsillectomy.

Figure 2. Skin Severity Score(SSS) in palms or soles after tonsillectomy (a) The 25%–75% percentile range and median value of the SSS in palms at each time point. (b) The 25%–75% percentile range and median value of the SSS in soles at each time point. (c) Kaplan–Meier curves of the time-dependent percentage change in a patient whose skin lesion in palms or soles disappeared after tonsillectomy (SSS of palms: black line, SSS of soles: gray line). (d) Kaplan–Meier curves of the time-dependent percentage change in a patient whose skin lesion in palms or soles improved ≥80% after tonsillectomy (SSS of palms: black line, SSS of soles: gray line).

Figure 3. The Pain Severity Score (PSS) after tonsillectomy. (a) The 25%–75% percentiles range and median value of the PSS at each time point. (b) Kaplan–Meier curves of the time-dependent percentage change in a patient whose PAO arthralgia disappeared (i.e., PSS = 0) after tonsillectomy. (c) Kaplan–Meier curves of the time-dependent percentage change in a patient with ≥80% improvement of the PAO arthralgia (i.e., PSS≤2) post-tonsillectomy.

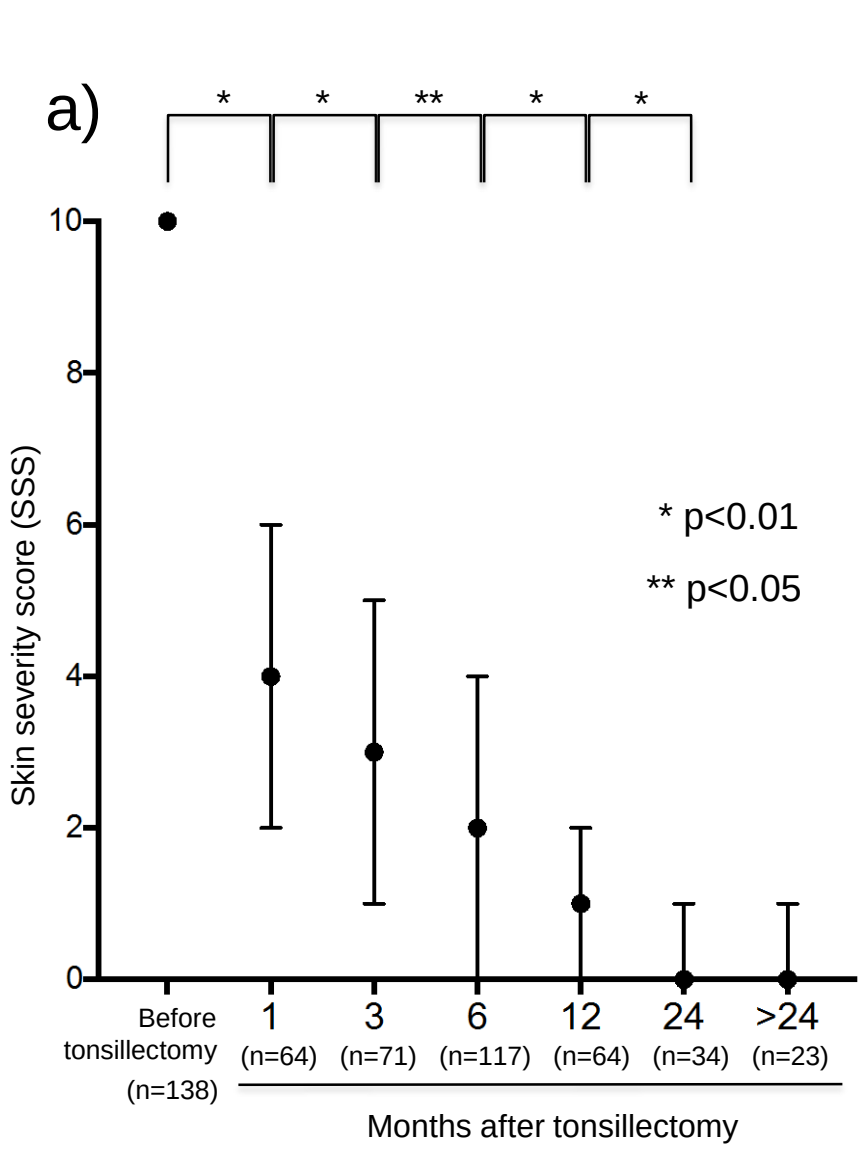
Figure 4. The Pustulosis Palmaris et Plantaris (PPP) Area and Severity Index (PPPASI) after tonsillectomy. (a) The 25%–75% percentile range and median value of the PPPASI at each time point. (b) The 25%–75% percentile range and median value of the improvement rate of the PPPASI (PPPASI%) at each time point. The PPPASI

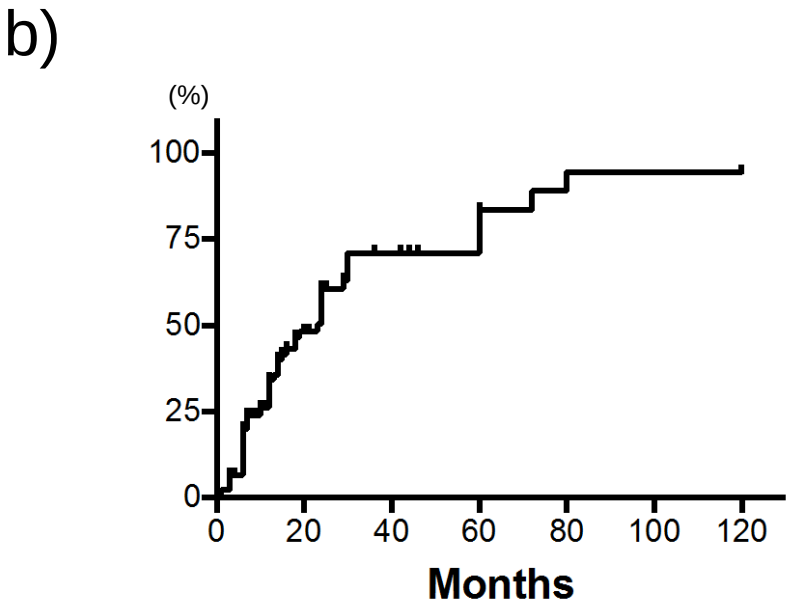
significantly decreased over time after tonsillectomy within the 24-month observation period. (c) Kaplan–Meier curves of the time-dependent percentage change of a patient in whom the skin lesion disappeared (i.e., PPPASI = 0) after tonsillectomy. (d) Kaplan–Meier curves of the time-dependent percentage change in a patient with ≥80% improvement in the skin lesion (i.e., PPPASI≥80%) after tonsillectomy.

Figure 5. Correlation among the SSS, PSS, and PPPASI%. (a) Correlation between the SSS and PPPASI% at six months after tonsillectomy (b) Correlation between the SSS and PPPASI% at last visit after tonsillectomy (c) Correlation between the PSS and PPPASI% at last visit after tonsillectomy. (d) Correlation between the PSS and SSS at the last visit after tonsillectomy.

PPP, pustulosis palmaris et plantaris; PPPASI, Pustulosis Palmaris et Plantaris Area and Severity Index; PPPASI%, improvement in the Pustulosis Palmaris et Plantaris Area and Severity Index; PSS, Pain Severity Score; SSS, Skin Severity Score

Figure 1


a)
* * ** * *
10
8
6
4
2
0
Skin severity score (SSS)
* p<0.01
** p<0.05
Before tonsillectomy (n=138)
1 (n=64)
3 (n=71)
6 (n=117)
12 (n=64)
24 (n=34)
>24 (n=23)
Months after tonsillectomy


b)
(%)
100
75
50
25
0
0 20 40 60 80 100 120
Months

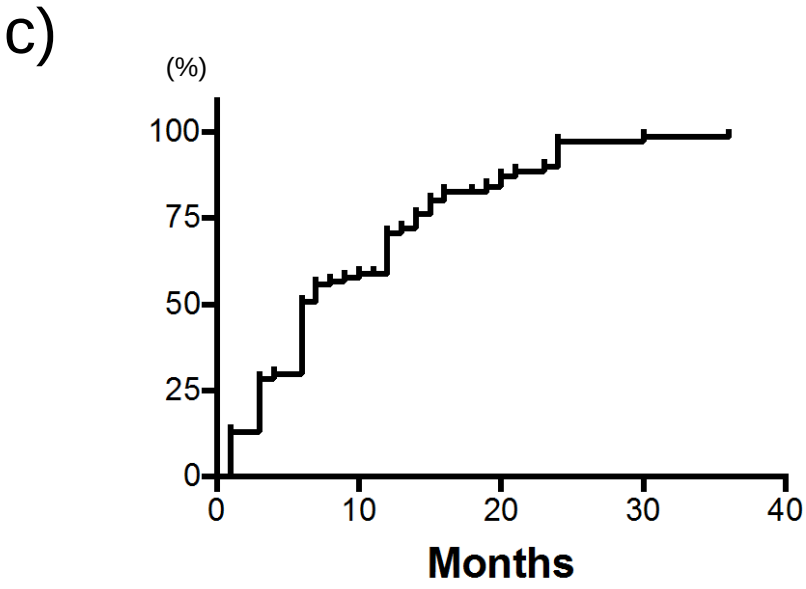

c)
(%)
100
75
50
25
0
0 10 20 30 40
Months

Figure 2

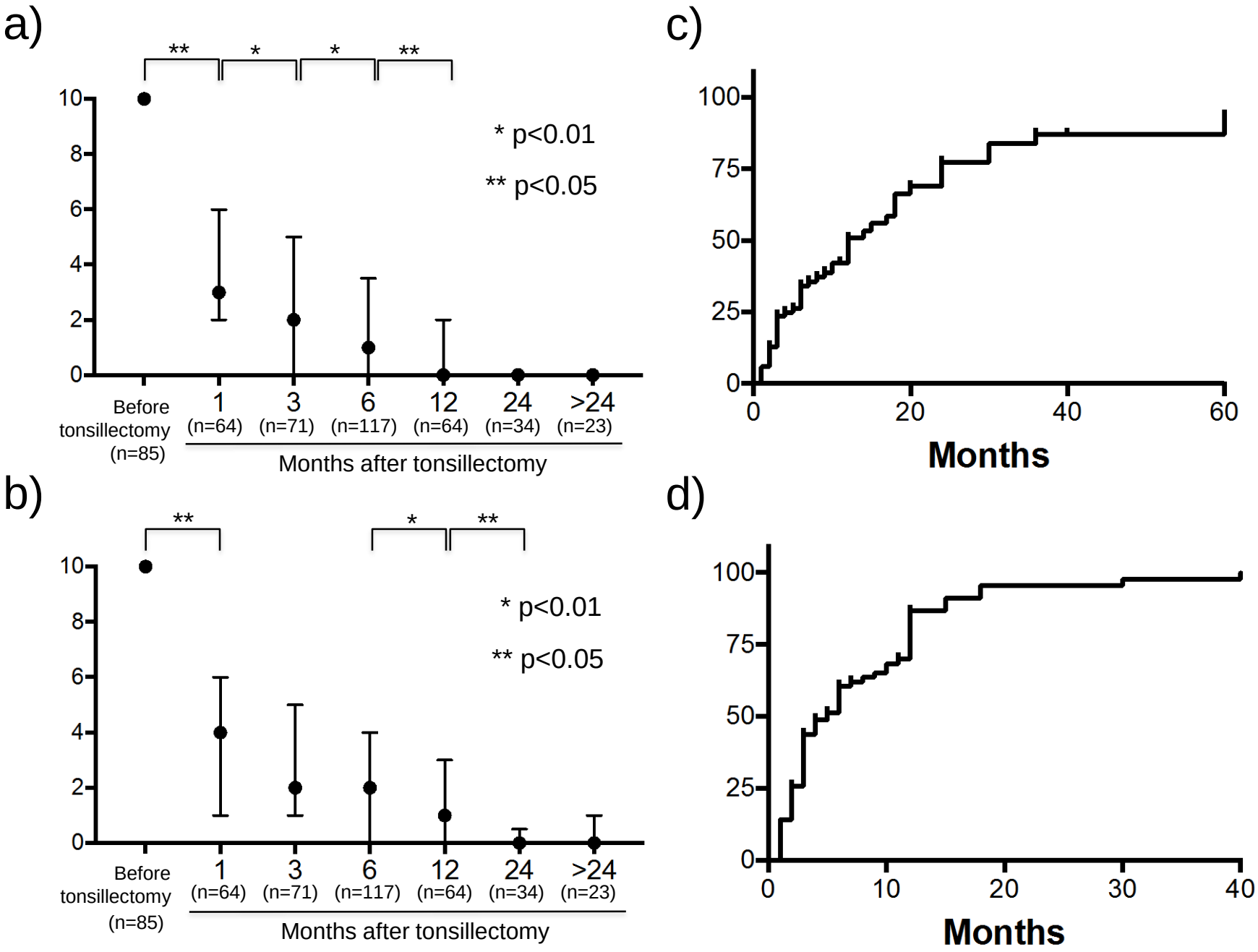
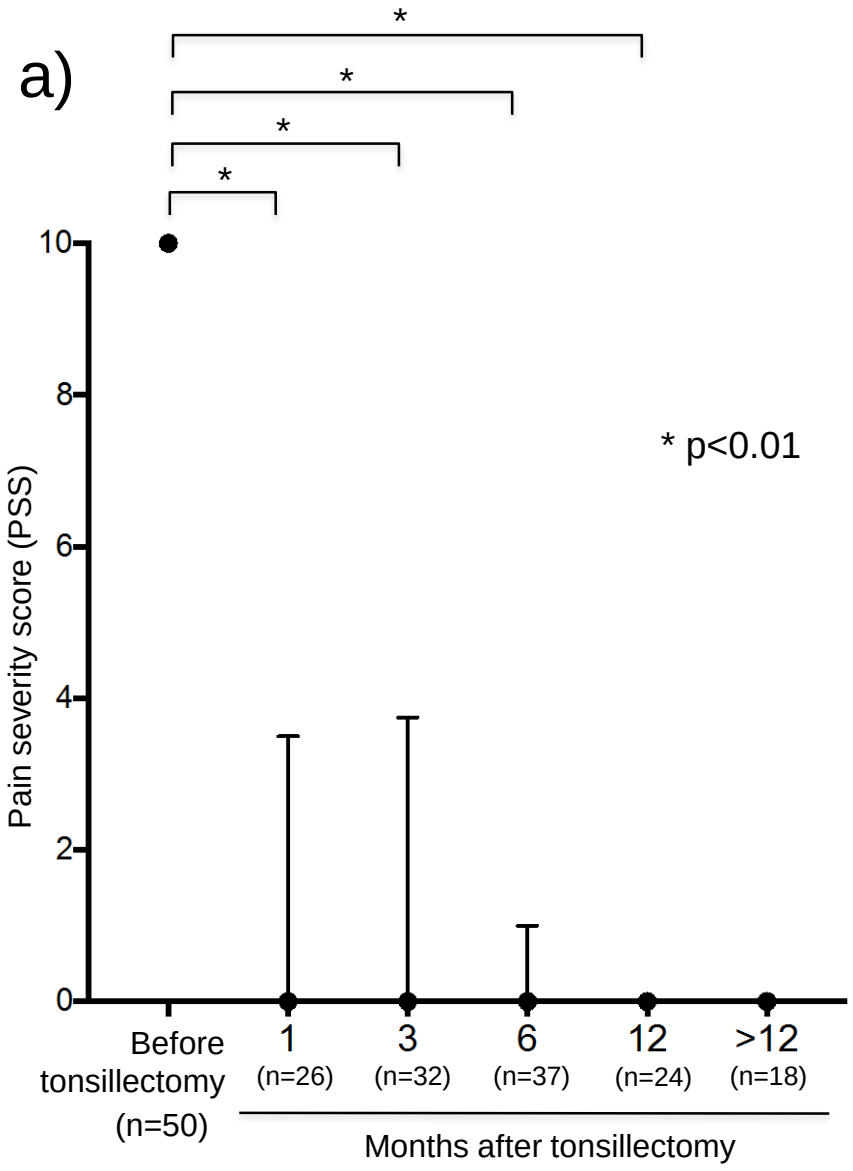
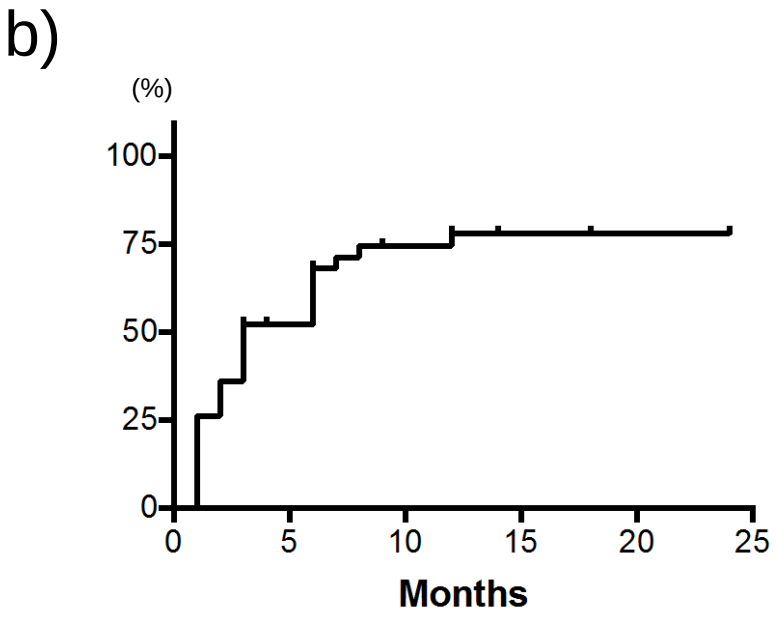

a)
**
*
*
**
10
8
6
4
2
0
* p<0.01
** p<0.05
Before tonsillectomy (n=85)
1 (n=64)
3 (n=71)
6 (n=117)
12 (n=64)
24 (n=34)
>24 (n=23)
Months after tonsillectomy
b)
**
*
**
10
8
6
4
2
0
* p<0.01
** p<0.05
Before tonsillectomy (n=85)
1 (n=64)
3 (n=71)
6 (n=117)
12 (n=64)
24 (n=34)
>24 (n=23)
Months after tonsillectomy
c)
100
75
50
25
0
0
20
40
60
Months
d)
100
75
50
25
0
0
10
20
30
40
Months

Figure 3


a)
*
*
*
*
10
8
6
4
2
0
Pain severity score (PSS)
* p<0.01
Before tonsillectomy (n=50)
1 (n=26)
3 (n=32)
6 (n=37)
12 (n=24)
>12 (n=18)
Months after tonsillectomy


b)
(%)
100
75
50
25
0
0
5
10
15
20
25
Months

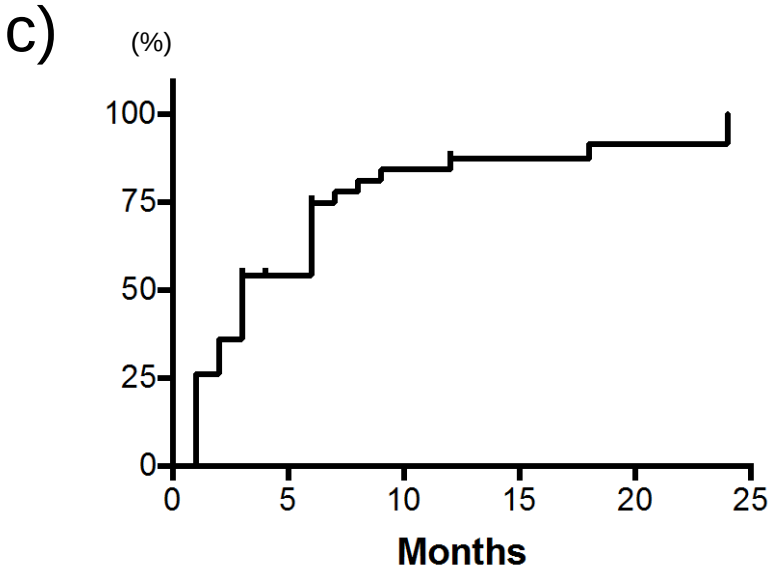
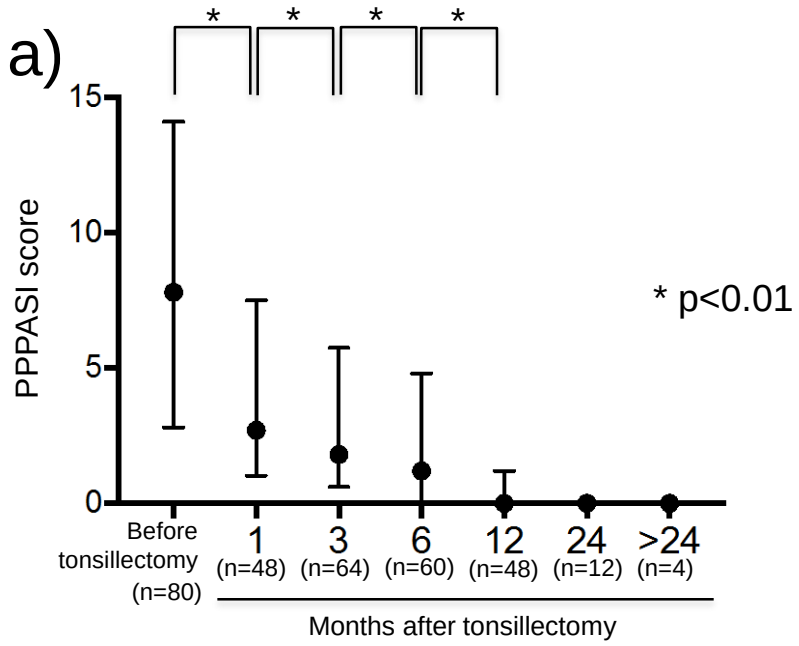
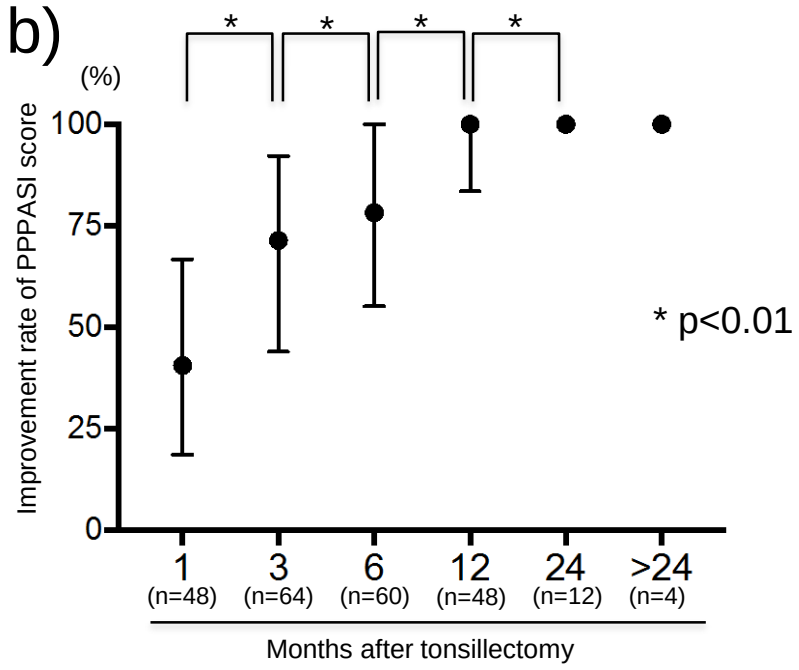
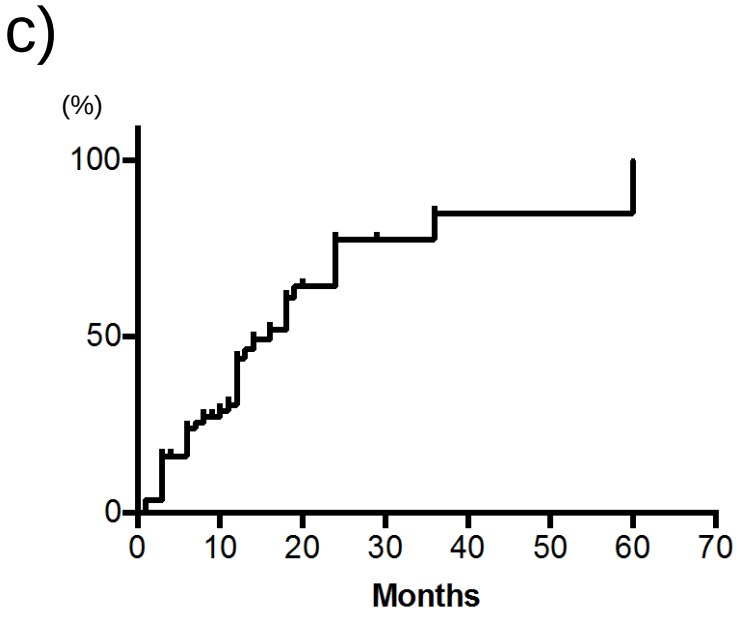

c)
(%)
100
75
50
25
0
0
5
10
15
20
25
Months

Figure 4


a)
*
*
*
*
15
10
5
0
PPPASI score
* p<0.01
Before tonsillectomy (n=80)
1 (n=48)
3 (n=64)
6 (n=60)
12 (n=48)
24 (n=12)
>24 (n=4)
Months after tonsillectomy


b)
*
*
*
*
(%)
100
75
50
25
0
Improvement rate of PPPASI score
* p<0.01
1 (n=48)
3 (n=64)
6 (n=60)
12 (n=48)
24 (n=12)
>24 (n=4)
Months after tonsillectomy


c)
(%)
100
50
0
0
10
20
30
40
50
60
70
Months

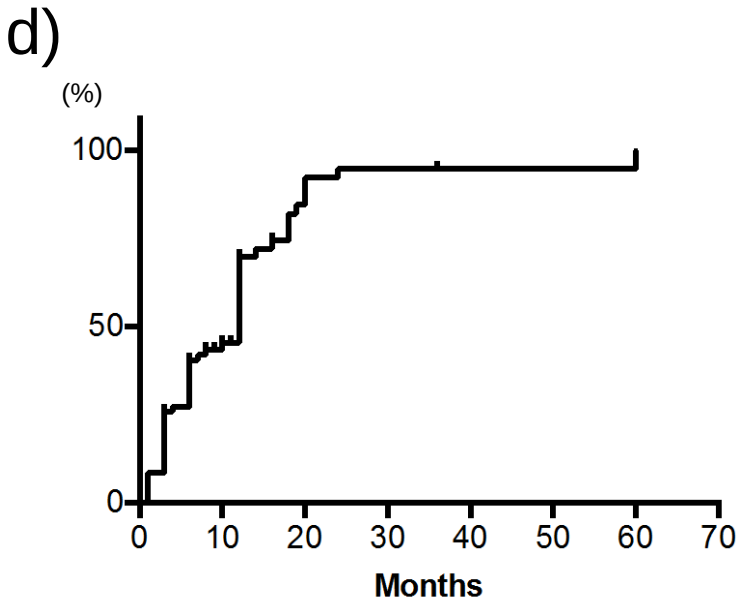

d)
(%)
100
50
0
0
10
20
30
40
50
60
70
Months

Figure 5

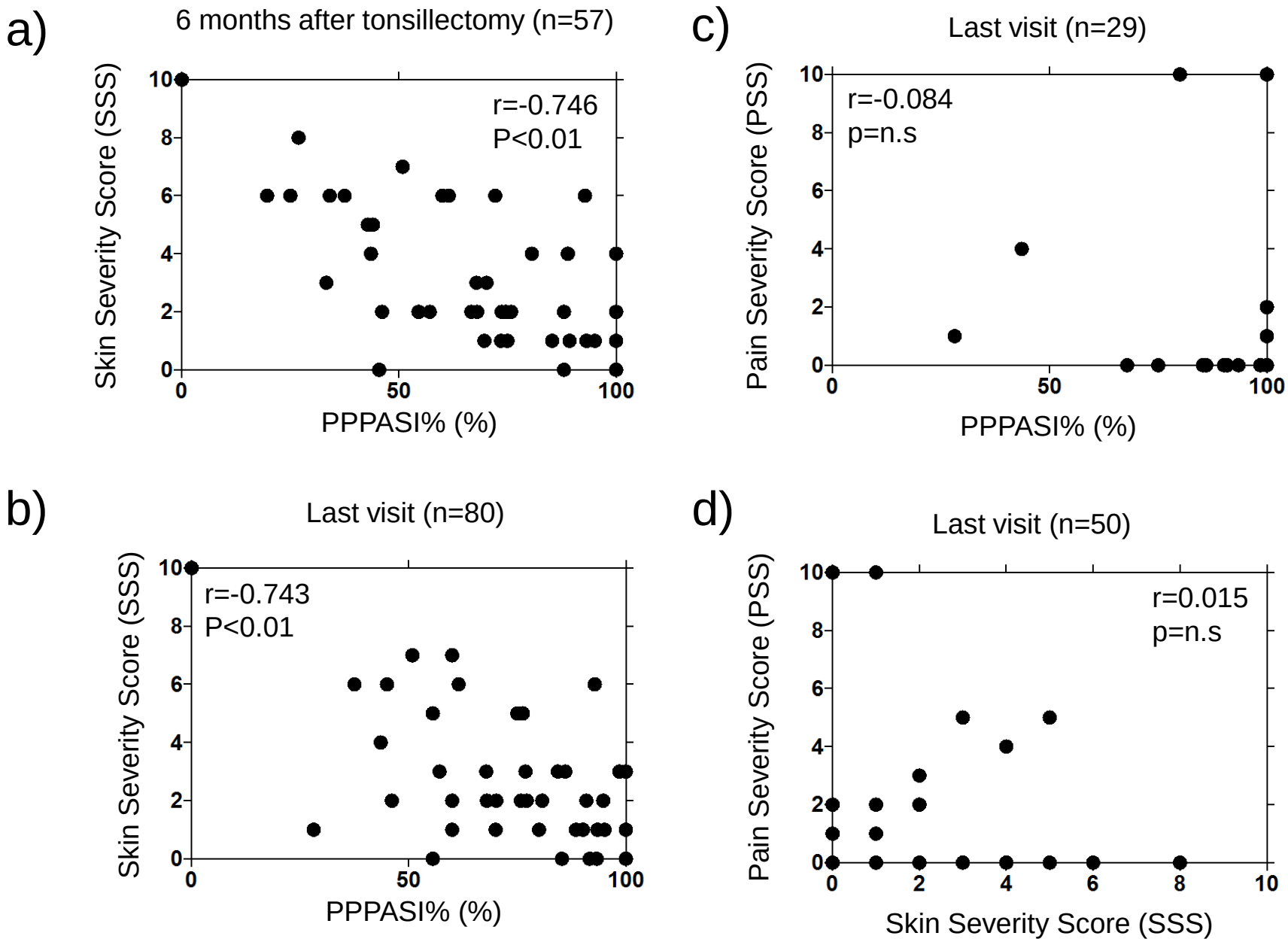

a)
6 months after tonsillectomy (n=57)
Skin Severity Score (SSS)
PPPASI% (%)
r=-0.746
P<0.01
b)
Last visit (n=80)
Skin Severity Score (SSS)
PPPASI% (%)
r=-0.743
P<0.01
c)
Last visit (n=29)
Pain Severity Score (PSS)
PPPASI% (%)
r=-0.084
p=n.s
d)
Last visit (n=50)
Pain Severity Score (PSS)
Skin Severity Score (SSS)
r=0.015
p=n.s

Table1. Clinical charactristics of the patients in each study

	SSS study	PSS study	PPPASI study
Total	138	50	80
Sex			
Male	33	16	23
Female	105	34	57
Age			
Years old (Median)	15-74(52)	15-74(49)	15-72(53)
Pustulotic Arthro-Osteitis (PAO)			
Presence	50	50	29
Absence	88	0	51
Period of having the disease before treatment			
Years (Median)	0-30 (3)	0-30 (4)	0-30 (2)
Deterioration in the PPP skin lesion or PAO arthralgia with an upper respiratory infection			
Yes	32	15	21
No	89	30	58
Smorker			
Yes	92	38	61
No	26	8	16
Tonsillar hypertrophy (Mackenzie)			
Ⅰ	82	29	49
Ⅱ	34	12	29
Serum level of Anti-streptolysin O antibody			
Positive	69	29	47
Negative	47	17	29
Deterioration in the PPP skin lesion or PAO arthralgia after tonsille			
Yes	65	23	47
No	35	14	23
Quitting smoking after tonsillectomy			
Yes	27	13	25
No	28	11	24
Obsevation period			
Months (Median)	3-120 (12)	3-60 (12)	3-120 (12)

SSS, Skin Severity Score; PSS, Pain Severity Score
; PPPASI, Palmoplantar Pustulosis Area and Severity Index

ect omy

Table2. Skin Severity Score(SSS) after tonsillectomy

	After tonsillectomy (months)						
	1	3	6	12	24	>24	last visit
Number of cases	64	71	117	64	38	24	138
Number of cases with SSS=0	3	12	30	28	21	16	60
Number of cases with SSS<2	20	34	70	57	36	23	106
Maximum of SSS	10	10	10	7	4	3	10
75% Percentile	6	5	4	2	1	1	2
Median of SSS	4	3	2	1	0	0	1
25% Percentile	2	1	0	0	0	0	0
Minimum of SSS	0	0	0	0	0	0	0

SSS, Skin Severity Score

Table3. Skin Severity Score(SSS) in palms or soles after tonsillectomy

	After tonsillectomy (months)						
	1	3	6	12	24	>24	last visit
Number of cases	51	66	61	50	29	15	85
Palms							
Number of cases with SSS=0	7	24	21	26	24	12	52
Number of cases with SSS>2	22	42	43	23	28	15	72
Maximum of SSS	10	10	10	5	5	1	10
75% Percentile	6	5	3.5	2	0	0	2
Median of SSS	3	2	1	0	0	0	0
25% Percentile	2	0	0	0	0	0	0
Minimum of SSS	0	0	0	0	0	0	0
Soles							

Table 4. Pain Severity Score(PSS) after tonsillectomy

	After tonsillectomy (months)					
	1	3	6	12	>12	last visit
Number of cases	26	32	37	24	18	50
Number of cases	19	21	27	19	15	36
Number of cases	19	22	30	21	18	43
Maximum of PSS	10	10	10	10	2	10
75% Percentile	3.5	3.75	1	0	0	1
Median of PSS	0	0	0	0	0	0
25% Percentile	0	0	0	0	0	0
Minimum of PSS	0	0	0	0	0	0

PSS, Pain Severity Score

Table 5. Palmoplantar Pustulosis Area and Severity Index(PPPASI) before and after tonsillectomy

	Before	After tonsillectomy (months)						
	tonsillectomy	1	3	6	12	24	>24	last visit
Case number	80	48	64	60	48	12	4	80
Number of cases with PPPASI=0		3	13	20	26	10	4	42
Number of cases with PPPASI≥80%		8	23	30	38	12	4	57
Maximum of PPPASI	51	30	17.6	15.2	10	1.2	0	15.2
75% Percentile	14.1	7.5	5.75	4.8	1.2	0	0	1.4
Median of PPPASI	7.8	2.7	1.8	1.2	0	0	0	0
25% Percentile	2.8	1.025	0.6	0	0	0	0	0
Minimum of PPPASI	0.2	0	0	0	0	0	0	0
Maximum of PPPASI%		100	100	100	100	100	100	100
75% Percentile		66.7	92.3	100	100	100	100	100
Median of PPPASI%		40.6	71.5	78.3	100	100	100	100
25% Percentile		18.6	44.1	55.2	83.6	100	100	76
Minimum of PPPASI%		-3.7	0	0	40	82.4	100	0

PPPASI, Palmoplantar Pustulosis Area and Severity Index

Table 6. Clinical factor correlated with PPPASI before tonsillectomy or presence of PAO

	Case Number	PPPASI before tonsillectomy (median)	p value		Case Number	Number of PAO cases	p value
Sex				Sex			
Male	23	1.2-51 (9.6)	ns	Male	33	16 (48%)	ns
Female	57	0.2-40.8 (7.2)		Female	105	34 (32%)	
Age (years old)				Age (years old)			
≥ 53	44	0.9-51 (7.05)	ns	≥ 51	69	27 (39%)	ns
< 53	36	0.2-40.8 (9.1)		< 51	69	23 (33%)	
Pustulotic Arthro-Osteitis (PAO)				Period of having the disease before treatment			
Presence	29	51-1 (7.8)	ns	≥ 3	72	32 (44%)	0.04
Absence	51	40.8-0.2 (8.4)		< 3	66	18 (27%)	
Period of having the disease before treatment				Deterioration in the PPP skin lesion with URI			
≥ 2 years	47	40.8-1 (8.4)	ns	Yes	32	15 (47%)	ns
< 2 years	33	51-0.2 (7.2)		No	89	30 (33%)	
Deterioration in the PPP skin lesion with URI				Smorker			
Yes	21	51-1 (10.4)	0.012	Yes	92	37 (40%)	ns
No	58	40.8-0.2 (6)		No	24	8 (31%)	
Smorker				Tonsillar hypertrophy (Mackenzie)			
Yes	61	51-0.2 (8.4)	0.048	Ⅰ	82	29 (35%)	ns
No	16	14.4-0.9 (3.9)		Ⅱ	34	12 (35%)	
Tonsillar hypertrophy (Mackenzie)				Serum level of Anti-streptolysin O antibody			
Ⅰ	49	51-0.2 (7.8)	ns	positive	68	28 (41%)	ns
Ⅱ	29	22.8-0.9 (8.4)		negative	47	18 (38%)	
Serum level of Anti-streptolysin O antibody				PPPASI			
positive	47	51-0.2 (7.8)	ns	≥ 7.8	42	16 (38%)	ns
negative	29	40-1 (7.2)		< 7.8	38	13 (34%)	
Deterioration in the PPP skin lesion after tonsillectomy				Deterioration in the PPP skin lesion after tonsillectomy			
Yes	47	51-0.2 (8.4)	ns	Yes	65	23 (35%)	ns
No	23	23.2-0.9 (6.2)		No	35	14 (40%)	
Quitting smoking after tonsillectomy				Quitting smoking after tonsillectomy			
Yes	25	20-0.2 (5.6)	0.036	Yes	28	13 (46%)	ns
No	24	51-1 (10.6)		No	27	12 (44%)	

PPPASI, Palmoplantar Pustulosis Area and Severity Index; PAO, pustulotic arthro-osteitis;

Table 7. Clinical factor affecting PPP skin lesion after tonsillectomy

		PPPASI = 0			PPPASI% ≥ 80%		
	Case Number	1-year rate (%)	2-year rate (%)	p value	1-year rate (%)	2-year rate (%)	p value
total	80	44.6	78.7		71	94.6	
Sex							
Male	23	29.7	100	ns	52.9	100	ns
Female	57	48.9	78.9		77.3	93.2	
Age (years old)							
≥ 53	44	49	79.9	ns	76.3	90.5	ns
< 53	36	38.2	76.8		63.9	100	
Pustulotic Arthro-Osteitis (PAO)							
Presence	29	59.3	86.5	ns	85	100	0.007
Absence	51	36.2	74.5		63	90.6	
Period of having the disease before treatment							
≥ 2 years	47	44	79.8	ns	63.7	95.4	ns
< 2 years	33	45.5	76.1		81.3	93.7	
Deterioration in the PPP skin lesion with an the upper respiratory infection							
Yes	21	39.6	91.6	ns	70.9	100	ns
No	58	48	67.3		71.9	91.6	
Smorker							
Yes	61	37.9	80.3	ns	67.9	96.8	ns
No	16	69	69		73.2	73.2	
Tonsillar hypertrophy (Mackenzie)							
Ⅰ	49	41.9	76.9	ns	74.2	93.1	ns
Ⅱ	29	52.3	82.1		73.1	95.5	
Serum level of Anti-streptolysin O antibody							
positive	47	37.8	77.4	ns	70.4	94.7	ns
negative	29	66.3	77.5		79.6	89.8	
PPPASI							
≥ 7.8	42	26.1	83.4	0.011	66.8	100	ns
< 7.8	38	66.7	73.4		76.3	85.8	
Deterioration in the PPP skin lesion after tonsillectomy							
Yes	47	43.9	78.3	ns	75.6	90.2	ns
No	23	54.2	84.7		81.6	100	
Quitting smoking after tonsillectomy							
Yes	25	61.9	84.8	0.033	84.8	95	ns
No	24	12.5	78.1		55.4	100	

PPPASI, Palmoplantar Pustulosis Area and Severity Index; PSS, Pain Severity Score; ns, not significant

Table 8. Univariate and multivariate analyses for cinical factor affecting PPP skin lesion after tonsillectomy

	PPPASI = 0					
	Univariate			Multivariate		
	HR	95% CI	p value	HR	95% CI	p value
Presence of Pustulotic Arthro-Osteitis (PAO)	1.727	0.913-3.223	0.092	5.226	1.840-16.607	0.002
Female	1.366	0.659-3.196	0.418			
Age ≥ 53	1.207	0.646-2.317	0.559			
Period of having the disease before treatment > 2 yerars	1.027	0.553-1.939	0.932			
Deterioration in the PPP skin lesion with URI	1.209	0.620-2.282	0.567			
Deterioration in the PPP skin lesion after tonsillect	0.725	0.366-1.513	0.379			
Smorker	0.775	0.382-1.741	0.515			
Mackenzie Ⅱ	1.406	0.751-2.606	0.283	0.839	0.340-2.009	0.695
High serum Anti-streptolysin O antibody (ASO) level	0.634	0.335-1.229	0.174	0.627	0.225-1.745	0.360
Quitting smoking after tonsillectomy	2.408	1.25-6.281	0.044	3.581	1.132-13.100	0.029
PPPASI ≥ 7.8	0.469	0.246-0.882	0.019	0.597	0.211-1.573	0.301

PPPASI, Palmoplantar Pustulosis Area and Severity Index; HR, hazard ratio; CI, confidence interval; URI, upper respiratory infection

	PPPASI% ≥ 80%					
	Univariate			Multivariate		
	HR	95% CI	p value	HR	95% CI	p value
Presence of Pustulotic Arthro-Osteitis (PAO)	1.897	1.105-3.226	0.021	2.977	1.341-6.960	0.007
Female	1.439	0.803-2.746	0.228	1.418	0.567-3.917	0.465
Age ≥ 53	0.889	0.525-1.513	0.661			
Period of having the disease before treatment > 2 yerars	0.811	0.478-1.389	0.439			
Deterioration in the PPP skin lesion with URI	1.121	0.624-1.935	0.694			
Deterioration in the PPP skin lesion after tonsille	0.758	0.428-1.384	0.428			
Smorker	0.844	0.44-1.787	0.638			
Mackenzie Ⅱ	1.054	0.613-1.794	0.846			
High serum Anti-streptolysin O antibody (ASO) level	0.613	0.352-1.091	0.095	0.634	0.266-1.586	0.320
Quitting smoking after tonsillectomy	1.474	0.748-1.983	0.263	1.400	0.624-3.225	0.416
PPPASI ≥ 7.8	0.756	0.447-1.289	0.299	0.788	0.351-1.720	0.553

PPPASI, Palmoplantar Pustulosis Area and Severity Index; HR, hazard ratio; CI, confidence interval; URI, upper respiratory infection