

1 Peritonsillar abscess may not always be a complication of acute tonsillitis: A prospective
2 cohort study

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4 Enni Sanmark¹, Johanna Wikstén, PhD¹, Hannamari Välimaa, PhD^{2,3}, Leena-Maija Aaltonen, Docent¹,
5 Taru Ilmarinen, PhD¹, Karin Blomgren, Docent¹

6 ¹ Department of Otorhinolaryngology - Head and Neck Surgery, Helsinki University Hospital, Finland

7 ²Department of Virology, University of Helsinki, Helsinki, Finland

8 ³Department of Oral and Maxillofacial Surgery, University of Helsinki and Helsinki University Hospital,
9 Helsinki, Finland

10

11 Corresponding author:

12 Enni Sanmark

13 E-mail: enni@sanmark.fi

14 Telephone number: +358408446940

15 Address: Töölönkatu 52 a11, 00250 Helsinki, Finland

16 ORCID: 0000-0003-0209-5501

17

18 Alternate author:

19 Johanna Wikstén

20 Department of Otorhinolaryngology - Head and Neck Surgery, Helsinki University Hospital, Finland

21 E-mail: johanna.wiksten@hus.fi

22 Telephone number: +358505957227

23 Address: Pohjoiskaari 37 a 1, 00200 Helsinki

24 ORCID: 0000-0001-9722-805X

25

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1 **ABSTRACT**

2 The present study aimed to specify diagnostics for peritonsillar abscesses (PTAs) and to clarify the role of
3 minor salivary glands. This prospective cohort study included 112 patients with acute tonsillitis (AT) and
4 PTA recruited at a tertiary hospital emergency department between February and October 2017. All
5 patients completed a questionnaire concerning their current disease. Serum amylase (S-Amyl) and C-
6 reactive protein (S-CRP) levels, tonsillar findings, and pus aspirate samples and throat cultures were
7 analyzed. Eight of 58 PTA patients (13.8%) had no signs of tonsillar infection. The absence of tonsillar
8 erythema and exudate was associated with low S-CRP ($p<0.001$) and older age ($p<0.001$). We also
9 observed an inverse correlation between S-Amyl and S-CRP levels (AT, $r=-0.519$; PTA, $r=-0.353$).
10 Therefore, we observed a group of PTA patients without signs of tonsillar infection who had significantly
11 lower S-CRP levels than other PTA patients. These findings support that PTA may be caused by an
12 etiology other than AT. Variations in the S-Amyl levels and a negative correlation between S-Amyl and
13 S-CRP levels may indicate that minor salivary glands are involved in PTA development.

14
15 **Abbreviations:** Peritonsillar abscess (PTA), acute tonsillitis (AT), Group A streptococcus (GAS),
16 *Fusobacterium necrophorum* (FN), *Streptococcus anginosus* group (SAG), incision and drainage (ID)

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18 **KEYWORDS:** Weber's glands; oral flora, CRP, amylase, smoking

19 **LEVEL OF EVIDENCE:** 1b

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26 **INTRODUCTION**

1 Acute tonsillitis (AT) is a highly prevalent infection that is responsible for a large number of
2 consultations. Peritonsillar abscess (PTA) is the most common deep head and neck infection, with an
3 incidence of 10 – 41/100,000 [1-5], and traditionally regarded as a purulent complication of AT, but the
4 evidence for an association between the two is uncertain. PTA may appear after tonsillectomy (TE)
5 without tonsillar remnants, as Windfuhr et al. demonstrated, and the seasonal incidence of the two entities
6 does not follow a symmetrical pattern [1, 6-8]. Over the last three decades, PTA has been speculated to
7 not necessarily arise from AT, but as a consequence of poor dental health, smoking, and salivary
8 dysfunction. Minor salivary glands have been suggested to play a significant role in PTA [3, 8, 9].
9
10 Shared symptoms of AT and PTA are sore throat and fever. PTA patients also suffer from trismus, and
11 the pain is typically asymmetrical [10, 11]. In both AT and PTA, common clinical findings include
12 tonsillar exudate and enlarged cervical lymph nodes. PTA patients also often have asymmetric
13 peritonsillar swelling [11, 12]. The diagnosis of AT and PTA is clinical, but a recent review
14 recommended measuring C-reactive protein (CRP) and performing a full blood count in all PTA patients,
15 though the benefits of laboratory tests in the diagnosis or treatment of PTA are unclear. As dehydration is
16 a common symptom of PTA, electrolytes should also be analyzed [2]. Tachibana et al. reported higher
17 serum leukocyte levels in PTA patients than AT patients, but did not observe differences in CRP levels.
18 In addition, higher serum CRP (S-CRP) levels predicted slower healing after PTA; the mean S-CRP in
19 PTA patients was 85 mg/l (1.3-380 mg/l) [13, 14].

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21 Salivary amylase levels can serve as a marker of salivary function, and recent studies have shown that
22 both serum and pus amylase levels are highly elevated in PTA patients compared to patients with other
23 neck abscesses and dental abscesses. In PTA patients, the mean serum amylase level is 50 U/l and mean
24 pus amylase level 3045 U/l (range 20–11,000 U/l) [15-17].

25
26 Group A streptococci (GAS) are the most prevalent bacteria causing both AT and PTA [9-11, 18].
27 Several studies have reported other bacteria (e.g., other beta-hemolytic streptococci [groups C and G] and

1 *Fusobacterium necrophorum* [FN]) as major pathogens in AT [19, 20], and FN has been recognized as a
2 major pathogen in PTA. In addition, *Streptococcus anginosus* group (SAG) streptococci have been
3 reported as important pathogens in peritonsillar infections and observed to predict the recurrence of PTA
4 [21, 22]. PTAs caused by FN are associated with significantly increased CRP and neutrophil levels
5 compared to PTAs caused by other pathogens [22].

6
7 Although the clinical picture of PTAs is diverse, previous studies concerning PTA diagnostics have
8 considered these patients as a uniform group. The aim of this study was to clarify the potential role of
9 minor salivary glands in the development of PTA and to specify diagnostics for PTA.

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11

12 **MATERIALS AND METHODS**

13 *Participants and samples*

14 The study included 112 patients referred to Helsinki University Hospital Department of
15 Otorhinolaryngology for AT or PTA between February and October 2017. Exclusion criteria were age
16 <15 years or pancreatic disease due to the changes in serum amylase levels caused by pancreatic
17 destruction [23]. Patients were divided into two subgroups based on clinical diagnosis: AT (n=54) or PTA
18 (n=58). All patients completed a questionnaire concerning their smoking habits, overall health, current
19 disease, prior antibiotics during the current infection, alcohol consumption, and previous tonsillar or
20 peritonsillar infections. The emergency department physician completed a structured form concerning
21 tonsillar findings, and the physicians evaluated the dental health and oral hygiene (good/poor) by
22 inspecting the oral cavity. Blood samples were collected from all patients, and S-CRP and serum amylase
23 (S-Amyl) levels were analyzed. The PTA patients were also treated with incision and drainage (ID). Pus
24 aspirate samples from PTA patients and throat swabs from AT patients were taken for bacterial culture.
25 Bacterial culture was performed at Helsinki University Hospital Laboratory Services (HUSLAB). Pus

1 samples were grown under both aerobic and anaerobic conditions and the superficial throat swabs under
2 aerobic conditions according to the laboratory's standard methods for diagnostic samples. The bacterial
3 culture results were recorded from the hospital laboratory database as reported by the diagnostic
4 laboratory. For the analysis, all isolates of beta-hemolytic streptococci, SAG and FN, *Haemophilus*
5 *influenzae*, *Staphylococcus aureus*, and heavy growth of *Neisseria meningitidis* were recorded as separate
6 isolates. Non-FN anaerobic isolates were combined and classified as other anaerobic bacteria. In addition,
7 the reported mixed normal flora was recorded as mixed regional flora.

8

9 *Ethical considerations*

10 All procedures that involved human participants were conducted in accordance with the ethical standards
11 of the institutional or national research committee and with the 1964 Declaration of Helsinki and its later
12 amendments or comparable ethical standards. The Ethics Committee of Helsinki University Hospital
13 approved the study protocol. All patients provided written informed consent prior to their participation.

14

15 *Main outcome measures*

16 Correlations between smoking, alcohol consumption, signs and symptoms of infection, laboratory tests,
17 oral health, and bacterial findings were analyzed and compared between the AT and PTA patients. The
18 main aim of these analyses was to determine whether any differences were present in laboratory tests, oral
19 health, or symptoms between AT and PTA patients. In addition, we examined whether different
20 subgroups of AT or PTA patients exist and whether laboratory values, bacterial findings, certain
21 symptoms, smoking, or oral health are related to a specific subgroup of patients.

22

23 *Statistical analysis*

24 Statistical analyses were performed using NCSS 8 statistical software (Hintze, J. [2012]; NCSS 8, NCSS,
25 LLC, Kaysville, UT, USA; www.ncss.com). The FN and FN+SAG groups were combined in the

1 statistical analysis due to the small number of patients in the groups. Numerical variables were analyzed
2 by the Mann-Whitney U-test and Kruskal-Wallis one-way ANOVA. Chi-squared was applied to compare
3 nominal variables. The Spearman rank-correlation was applied to two numerical variables with non-
4 normal distribution. *P*-values <0.05 were considered significant.

7 **RESULTS**

8 A total of 112 patients were included in the study. Patient characteristics and clinical data are presented in
9 Table 1. None of the patients developed a complication during the first 3 months.

10 11 *Serum amylase and C-reactive protein levels*

12 A significant inverse correlation was observed between S-Amyl (normal reference 28-100 U/l) and S-
13 CRP (normal reference 0.05-3 mg/l) levels in both the AT and PTA groups (AT, $r = -0.519$, $p \leq 0.001$;
14 PTA, $r = -0.353$, $p \leq 0.001$; Fig 1). We found no differences in the S-Amyl or S-CRP levels between the
15 AT and PTA groups (S-Amyl, $p = 0.767$; S-CRP, $p = 0.501$). Alcohol consumption and smoking habits had
16 no effect on S-Amyl levels (alcohol, $p = 0.750$; smoking, $p = 0.205$). No correlation was found between age
17 and CRP (AT and PTA patients $r = -0.094$, $p = 0.342$; PTA patients $r = -0.137$, $p = 0.329$). The S-Amyl and
18 S-CRP levels in AT and PTA patients are presented in Table 2.

19 20 *Tonsillar findings*

21 In patients with AT, the presence of tonsillar erythema, tonsillar exudate, or both had no effect on S-Amyl
22 ($p = 0.306$) or S-CRP ($p = 0.363$) levels. In the PTA group, eight patients did not have tonsillar erythema or
23 tonsillar exudate. These eight PTA patients had significantly lower S-CRP levels (median 15 mg/l, range
24 3-40 mg/l) than PTA patients presenting with tonsillar findings (median S-CRP 60 mg/l, range 3-313
25 mg/l; $p < 0.001$). S-Amyl levels were slightly, but not significantly ($p = 0.190$), higher in these eight patients
26 (median 49 U/l, range 27-82 U/l) compared to the other PTA patients (median 41 U/l, range 15-116 U/l;
27 Fig 2). PTA patients without tonsillar findings were significantly older (median age 50.5 years, range 24-

1 65 years) than the other PTA patients (median age 34 years, range 16-60 years; $p=0.006$). Of the 58
2 PTAs, two (3.4%) were bilateral. Oral health had no impact on bacterial findings in either group.

3

4 *Bacterial findings*

5 Bacterial samples were taken from all but two PTA patients. The bacterial findings are presented in Table
6 3. The most common bacteria isolated in AT patients were GAS (41.7% of all samples), group B, C, and
7 G beta-hemolytic streptococci (3.7%), and *H. influenzae* (3.7%). In 51.9% of AT patients, only normal
8 mixed tonsillar flora was reported. In PTA patients, anaerobic Gram-negative rods were a common
9 finding ($n=27$, 37.5% of all samples), including FN isolated from five patients. GAS and SAG were
10 isolated from an almost equal number of samples (18.1% vs. 15.3%). In three samples, SAG was found
11 together with FN. *H. influenzae*, *N. meningitidis*, and *S. aureus* isolates were found together with
12 anaerobic Gram-negative rods. *N. meningitidis* growth was heavy and included as a separate finding. One
13 bacterial sample in the PTA group was negative.

14

15 The bacteria isolated from the eight PTA patients without tonsillar findings were GAS ($n=2$), *S. aureus*
16 ($n=2$), FN ($n=1$), anaerobic Gram-negative rods ($n=5$), and mixed aerobic flora ($n=1$). *S. aureus* was
17 isolated together with anaerobic Gram-negative rods in both cases. All of these bacteria were also isolated
18 in other PTA patients; therefore, we found no obvious difference between the two groups in the bacterial
19 etiology of the disease.

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21 No differences were found in the S-Amyl or S-CRP levels between the bacterial findings in either the AT
22 or PTA group (AT, S-Amyl $p=0.620$, S-CRP $p=0.331$; PTA, S-Amyl $p=0.925$, S-CRP $p=0.203$). Bacterial
23 findings were not associated with any of the recorded specific symptoms (unilaterality, absence of
24 common cold, fever) or presence of tonsillar erythema or exudate in the AT or PTA group. Oral health
25 had no impact on bacterial findings in either group.

26

1 In patients treated with prior antibiotics, SAG was found more frequently than other bacteria ($p=0.037$).
2 Patients with SAG were significantly older (median age 45 years, range 27-53 years) than patients with
3 the following other bacteria: GAS (median age 30 years, range 20-58 years), non-SAG/beta-hemolytic
4 streptococci/FN (median age 31.5 years, range 18-65 years), or FN and FN+SAG (median age 25.5 years,
5 range 16-37 years; $p=0.022$). Seven out of nine patients (77.8%) with SAG were male.

7 **DISCUSSION**

8 Some of the PTA patients in this study had no tonsillar findings at clinical examination. In contrast, all
9 AT patients had tonsillar erythema, tonsillar exudate, or both. PTA patients presenting without tonsillar
10 erythema and tonsillar exudate had significantly lower S-CRP levels than PTA patients with tonsillar
11 findings. These eight patients without tonsillar findings were also older than other PTA patients. Thus,
12 patient characteristics, S-CRP, S-Amyl, and clinical findings may be tools for differentiating PTA patient
13 subgroups with different etiological factors [3, 5]. In addition, we found an inverse correlation between S-
14 Amyl and S-CRP levels and lower S-CRP and higher S-Amyl levels in afebrile AT patients compared to
15 those with fever.

17 *Strengths and limitations of the study*

18 This prospective study is the first study to compare both S-CRP and S-Amyl between AT and PTA
19 patients, as well as between patients with different signs and symptoms of infection. One limitation of this
20 study is that only aerobic bacteria were analyzed in superficial throat bacterial cultures. In addition,
21 though both aerobes and anaerobes were tested in pus samples, some bacterial findings were so few that it
22 limited the statistical analysis. We did not exclude AT patients with earlier PTA ($n=3$) from the study,
23 which could have affected the results, but our cohort included very few of these patients. Patients with
24 alcohol abuse and pancreatic disease were excluded from the study, and none of the patients were
25 pregnant, but patients with other conditions causing elevated S-Amyl, such as gastrointestinal tract
26 infections, eating disorders, drug use, renal dysfunction, and macroamylasemia, were not excluded.
27 Furthermore, the evaluation of tonsillar findings (erythema, exudate) was based on subjective observation

1 by ear, nose, and throat physicians. However, due to prospective nature of the study, as well physicians'
2 substantial experience with tonsillar diseases, the evaluation can be considered reliable. Oral health was
3 also evaluated by an ear, nose, and throat physician, not a dentist, and classified only as good/poor. We
4 used the standard reference values to analyze S-Amyl and did not have the baseline S-Amyl value for the
5 112 patients. Therefore, it is impossible to determine the actual change in S-Amyl values caused by the
6 infection. Our material is consistent with previous studies concerning patient age, gender, oral health, and
7 smoking habits [2, 9, 19, 24].

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10 *Comparison with other studies*

11 No earlier studies have compared S-CRP and S-Amyl levels between PTA patients with different signs
12 and symptoms. In our study, we observed a group of PTA patients without tonsillar findings. Compared
13 to patients with AT or PTA with tonsillar findings, these patients had lower S-CRP levels and were older.
14 In AT and PTA patients, an inverse correlation between S-Amyl and S-CRP levels was evident. Similar
15 findings have been reported in patients with infection of major salivary glands. Saarinen et al.
16 demonstrated that the majority of patients suffering from parotitis had elevated S-Amyl levels (median
17 261 U/l, range 24-1220), but only half of the patients had significantly elevated S-CRP levels >40 mg/l;
18 32% of the patients had normal S-CRP < 5 mg/l (median 13.0 mg/l, range 5-170 mg/l) [25]. These similar
19 findings between our eight PTA patients and patients with confirmed infection of the major salivary
20 glands suggests that the PTA in these eight patients was due to infection of the minor salivary glands [25-
21 28]. One possible reason that S-Amyl levels in PTA patients remain below the reference values is the
22 small size of the minor salivary glands relative to major salivary glands, which prevents the elevation
23 from becoming substantial. In addition, S-Amyl reference values are validated for the diagnosis of
24 pancreatic diseases and may not be directly adaptable to reflect the activity of minor salivary glands. For
25 a more reliable analysis of changes in S-Amyl in PTA patients, we should define the baseline S-Amyl
26 levels in these patients and prefer S-Amyl measurements over salivary amylase.

27

1 We found no difference in S-Amyl levels between patients with and without a history of recurrent AT or
2 PTA. This observation differs from an earlier study demonstrating significantly lower pus amylase levels
3 in patients with a recurrent PTA [16]. Tachibana et al. previously showed no difference in S-CRP levels
4 between AT and PTA patients. Our observations were similar [14].

5
6 We also observed that afebrile AT patients have lower S-CRP and higher S-Amyl levels than AT patients
7 with fever. One could speculate that salivary gland activation sometimes occurs in AT, though this
8 hypothesis has not been presented previously [4, 29]. AT patients with unilateral symptoms had lower S-
9 CRP and higher S-Amyl levels than patients with bilateral throat pain, which could also indicate activity
10 in the minor salivary glands. We compared S-Amyl levels between PTA and AT patients and did not
11 observe a difference between the groups. El Saied et al. previously demonstrated a difference in both
12 serum and pus amylase levels between PTA patients and patients with deep neck abscesses and dental
13 abscesses [16, 17].

14
15 In our study, GAS was the most prevalent bacterial finding in PTA patients, followed by SAG and FN. In
16 a recent Danish study of PTA, FN was the predominant pathogen, GAS was the second most common,
17 and group C *Streptococcus* was the third [22]. In this study, SAG was found in older patients and
18 predominately in males. Furthermore, SAG has been shown to predict the rapid recurrence of PTA and to
19 be found in older male patients [21, 30].

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21 *Clinical applicability of the study*

22 Our results suggest that the pathogenesis of PTA may differ between patients; thus, patient
23 characteristics, S-CRP and amylase levels, and clinical findings may be useful tools for differentiating
24 these PTA subgroups. For example, when differentiating between subgroups of PTA patients, we could
25 identify patients who would benefit from TE after the first PTA episode. Further studies are needed to
26 clarify the usability of these variables and their significance in helping choose the optimal treatment
27 strategy for different PTA patients.

1

2 **CONCLUSION**

3 The etiology of PTA is not as unambiguous as previously thought. Bacteria may not be the only factor
4 determining the course of the disease. There seems to be a subgroup of PTA patients without signs of
5 tonsillar infection that share features with parotitis. Therefore, it may be possible for PTA in these
6 patients to not begin as a complication of AT, but as an infection of the minor salivary glands. More
7 research is needed to examine the different subgroups of PTA and the role of minor salivary glands in
8 PTA and AT.

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1 **FIGURE LEGENDS**

2
3 **Fig 1. Correlation between serum amylase and C-reactive protein levels.**

4 (A) Patients with acute tonsillitis ($r=-0.519$, $p\leq 0.001$). (B) Patients with peritonsillar abscess ($r=-0.353$, $p\leq 0.001$).

5 **Fig 2. Distribution of serum proteins in PTA patients with different tonsillar findings.**

6 (A) C-reactive protein (S-CRP) and (B) amylase (S-Amyl). 1, tonsillar erythema; 2, tonsillar exudate; 3, no findings; 4,
7 tonsillar erythema and exudate.

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1 Table 1. Patient characteristics.
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Characteristic	All PTA patients (n=58)	AT patients (n=54)	PTA patients without tonsillar findings (n=8)
Age, years			
Median	36	28.5	50.5
Range	16–65	15–86	24–65
Gender			
Male	36 (62.1)	21 (38.9)	5 (62.5)
Female	22 (37.9)	33 (61.1)	3 (37.5)
Smoking			
Non-smoker	21 (36.8)	20 (37.0)	5 (62.5)
Smoker	24 (41.4)	22 (40.7)	2 (25.0)
Ex-smoker	12 (20.7)	12 (22.2)	1 (12.5)
No information	1		
Alcohol consumption			
Yes			
No	36 (62.1)	31 (57.4)	4 (50.0)
No information	21 (36.2)	23 (42.6)	4 (50.0)
	1		
Prior antibiotics for more than 24 hours			
Yes	10 (17.2)	9 (16.7)	1 (12.5)
No	48 (82.8)	45 (83.3)	7 (87.5)
Duration of symptoms ^a prior to PTA			
1-3 days			
>3 days	16 (27.6)	28 (51.9)	2 (25.0)
	42 (72.4)	26 (48.1)	6 (75.0)
Unilateral throat pain			
Yes	54 (93.1)	31 (60.8)	8 (100.0)
No	4 (6.9)	20 (39.2)	0 (0)
No information		3	

Fever			
Yes	38 (65.5)	41 (75.9)	3 (37.5)
No	20 (34.5)	13 (24.1)	5 (62.5)
Symptoms of common cold			
Yes			
No	16 (27.6)	23 (44.2)	2 (25.0)
No information	42 (72.4)	29 (55.8)	6 (75.0)
		2	
Prior tonsillar infection			
AT	13 (22.8)	12 (22.2)	0(0)
CT	1 (1.8)	1 (1.9)	0 (0)
PTA	8 (14.0)	2 (5.6)	2 (25.0)
None	35 (61.4)	38 (70.4)	6 (75.0)
No information	1		
Tonsillar findings			
Exudate			
Erythema	16 (28.1)	16 (30.2)	0 (0)
Both	26 (45.6)	16 (30.2)	0 (0)
None	7 (12.3)	21 (39.6)	0 (0)
No information	8 (14.0)	0 (0)	8 (100.0)
	1		
Oral hygiene			
Good			
Poor	52 (91.2)	48 (90.6)	7 (87.5)
No information	5 (8.8)	5 (9.4)	1 (12.5)
	1	1	

1 Data are presented as n (%) unless otherwise noted. PTA, peritonsillar abscess; AT, acute tonsillitis; CT,
2 chronic tonsillitis

3 ^a Throat pain, fever, hoarseness.
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Table 2. Serum amylase and CRP levels in AT (n=52) and PTA (n=54) patients with different infection symptoms.

	Median amylase in AT (U/l)	Median CRP in AT (mg/l)	Median amylase in PTA (U/l)	Median CRP in PTA (mg/l)
Fever				
Yes	37.5	104.5	44	82
No	65.5	15	46	40
p-value	0.0212	0.00037	0.637	0.239
Symptom duration				
<3 days	39	94	36	74
>3 days	42	80	44	59
p-value	0.650	0.063	0.655	0.720
Unilateral pain	46	75.5	44	60
Bilateral pain	30.5	110	32.5	120.5
p-value	0.033	0.031	0.175	0.522
Common cold				
Yes	41	94	51	36
No	38.5	90	41	82
p-value	0.914	0.575	0.0096	0.0755
Oral hygiene				
Normal/Good	39.5	87	41	67
Poor	42	92	48	36
p-value	0.862	0.874	0.484	0.447
History of				
AT	34	90	46	105
PTA			35	36
None	44	83	44	56
p-value	0.151	0.971	0.852	0.409

5 AT, acute tonsillitis; PTA, peritonsillar abscess

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Table 3. Bacterial findings in patients with AT or PTA.

Variable		AT ^a	PTA
Number of samples		54	56
Bacterial findings, n (%)			
Aerobic bacteria			
Beta-hemolytic streptococci		24 (44.4)	16 (22.2)
	Group A streptococci	22 (40.7)	13 (18.1)
	Group B, C, or G streptococci	2 (3.7)	3 (4.2)
<i>Streptococcus anginosus</i> group		0 (0)	11 (15.3)
<i>Haemophilus influenzae</i>		2 (3.7)	1 (1.4)
<i>Neisseria meningitidis</i>		0 (0)	1 (1.4)
<i>Staphylococcus aureus</i>		0 (0)	3 (4.2)
Other aerobic bacteria		0 (0)	0 (0)
Anaerobic bacteria			
<i>Fusobacterium necrophorum</i>			5 (6.9)
Other anaerobic bacteria ^b			22 (30.6)
Mixed regional flora		28 (51.9)	13 (18.1)

1

2 AT, acute tonsillitis; PTA, peritonsillar abscess

3 ^a Only aerobic culture was performed for patients with acute tonsillitis (AT).

4 ^b Other anaerobic bacteria isolated: anaerobic Gram-negative rods (n=14), *Prevotella* species (n=2),
5 *Fusobacterium* species other than necrophorum (n=4), anaerobic mixed flora (n=2).

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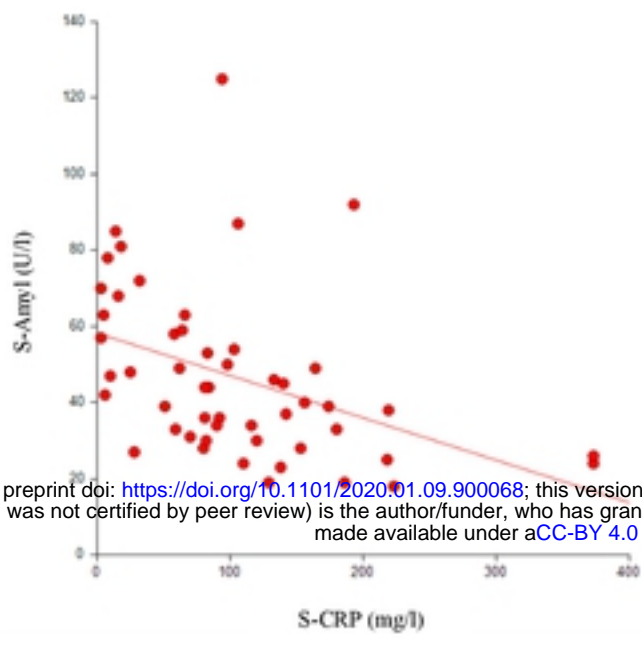
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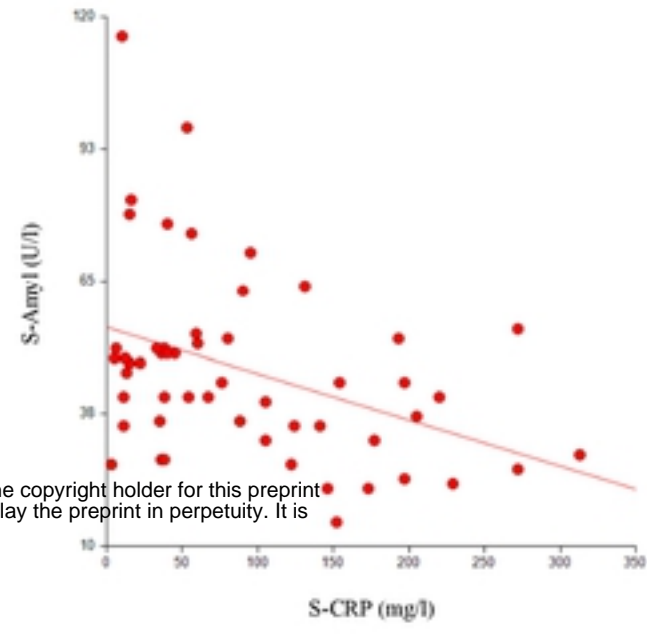
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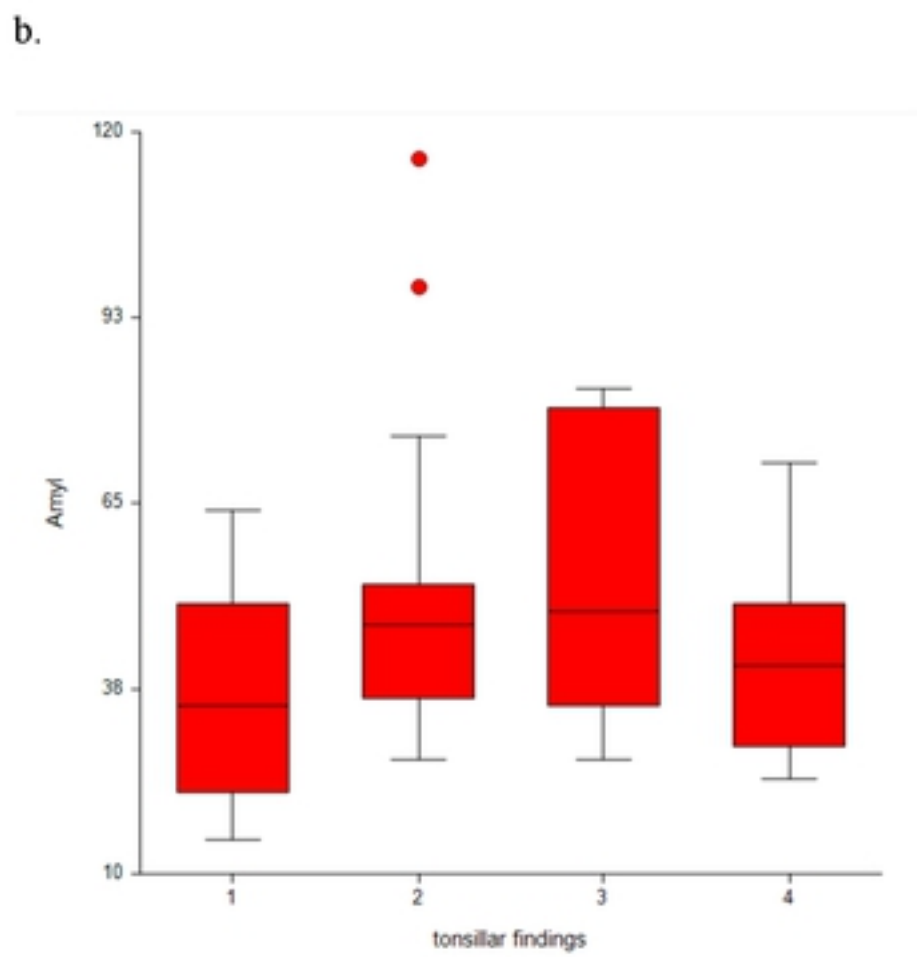
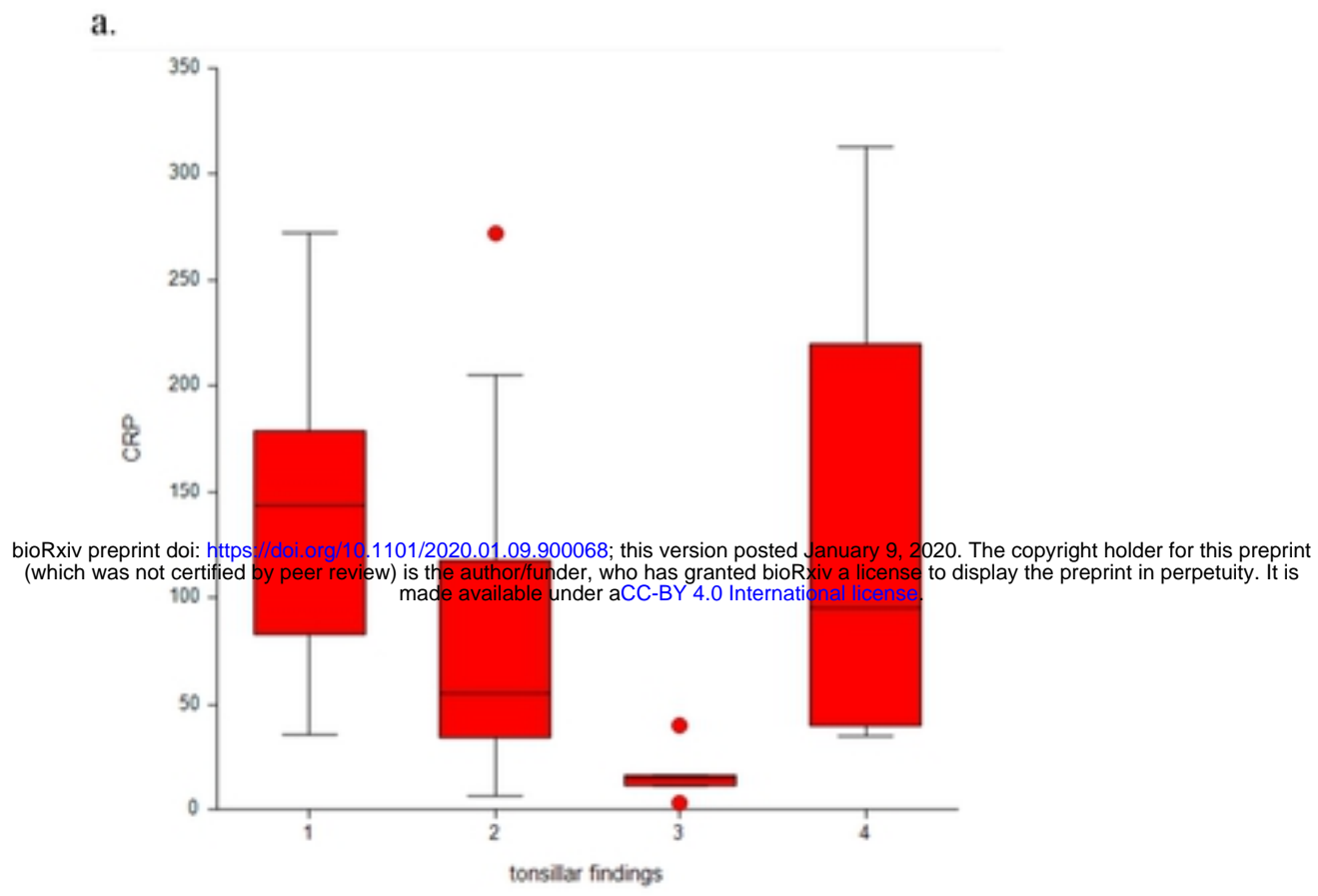
a)



b)



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