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Original Article

What factors predict craniomandibular disorders in severe COVID-19 survivors after prolonged intubation?

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ABSTRACT

Purposes: To estimate and identify predictors of craniomandibular disorders (CMDs) in severe COVID-19 survivors after prolonged intubation ≥ 1 week (SCOVIDS-PI).
Methods: This retrospective study enrolled two cohorts of SCOVIDS-PIs with *vs.* without CMD during a one-year period. The predictor variables were demographic, dental, anesthetic, and laboratory parameters. The main outcome was presence of CMD until six post-PI months (yes/no). Appropriate statistics were computed with α = 95%.
Results: The sample comprised 176 subjects aged 59.2 ± 17.2 years (range, 27–89; 11.9% with CMDs; 30.1% females). CMDs were significantly associated with *(1)* bilateral posterior tooth loss (P = 0; number needed to screen [NNS] = 1.6), *(2)* dentofacial skeletal class II/convex face (P = .01; NNS = 2.2), and *(3)* peak CRP during intensive care ≥ 40 mg/l (P = .01; NNS = 3.5). With combined predictors, NNS became 2 to 4.3.
Conclusions: Three predictors of CMDs in SCOVIDS-PIs: bilateral molar loss, convex face, and CRP ≥ 40 mg/l, indicate CMD screening and/or referral to a CMD specialist, regardless of patients' age, gender, underlying CMDs, or previous dental checkups. Screening ~2 to 4 "SCOVIDS-PIs with ≥ one predictor" will identify one CMD events/patients during the first six post-PI months.

1. Introduction

Craniomandibular disorders (CMDs) are together shaped by multiple predisposing or precipitating factors and/or co-morbidities. They can be myogenic, arthrogenic, occlusogenic, or with co-morbidities (*e.g.* autoimmune diseases). In 2020, the International Headache Society and its collaborators launched the International Classification of Orofacial Pain, 1st Edition, describing 9 myogenic and 13 temporomandibular joint (TMJ) arthrogenic types. TMJ injury is an important risk factor of CMDs [1–3].

During orotracheal intubation (OTI), TMJ rotation-translation maneuvers by the anesthesiologist to reach the patient's maximal mouth opening and atraumatic passage for OTI may injure the TMJ due to excessive forces applied manually or with the laryngoscope.

Abbreviations: ACE2, Angiotensin-converting enzyme 2; CI, Confidence interval; CMD, Craniomandibular disorders (also called, temporomandibular disorders); CRP, C-reactive protein; COVID-19, Coronavirus disease 2019; DGFDT, The German Association for Functional Diagnostics and Therapy of the TMJ; ICU, Intensive care unit; MVPs, Mechanically ventilated patients; NNS, Number needed to screen; OCEBM, The Oxford center for Evidence-Based Medicine; $OR_{adj.}$, Adjusted odds ratio; OTI, Orotracheal intubation; PI, Prolonged intubation; RANK, Nuclear factor κ B; RANKL, Nuclear factor κ B-Ligand (system); RR, Relative risk; r_s, Spearman rho (of ranked-order correlation coefficients); SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; SCOVIDS-PI, Severe COVID-19 survivors after prolonged intubation ≥ 1 week; STROBE, The *ST*rengthening the *R*eporting of *OB*servational studies in *E*pidemiology (guidelines); TMJ, Temporomandibular joint; Trp-Kyn, Tryptophan-kynurenine (pathway)

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Time span of the TMJ in a "stressed" position, *i.e.* prolonged intubation (PI), further intensifies the damage. Loss of muscle tone due to anesthetics can increase joint mobilization [2–5]. In a prospective study (n = 40), laryngoscopic tracheal visualization caused massive (pathologic) TMJ distraction from its physiological position/movement, and one patient (or 2.5%) was reported to have tear of the lateral ligament of the TMJ [5]. Another prospective study (n = 200) revealed significant reduced mouth opening within the first post-OTI week in 45 patients (or 22.5%) [6]. Albeit controversial, OTI especially PI is recognized as one risk factor for development and/or exacerbation of CMDs with facial pain [2–6].

The purpose of this study was to answer the following research question: "Among severe COVID-19 survivors after PI ≥ 1 week (SCOVIDS-PIs), what factor is associated with CMDs up to six post-PI months?" The investigators hypothesized that there is a set composed of ≥ 1 risk factor that may guide clinicians through CMD screening and/or patient referral to the CMD specialist. The specific aims of this study were to 1) estimate the frequency of CMD in SCOVIDS-PIs, 2) identify the risk factors, and 3) calculate number needed to screen (NNS) of all identified predictors. At the end, this study will provide the 2011 Oxford center for Evidence-Based Medicine (OCEBM)'s Level of Evidence **"3"**, and recommendation grade: **"B".**

2. Materials and methods

2.1. Study design/population

This was a retrospective chart-review evaluation of two eligible SCOVIDS-PI cohorts treated at a "pooled" intensive care unit (ICU; a "cohort" ICU ward for COVID-19 patients) of a German medical center in a COVID-19 "hot spot" area during a one-year period. Despite many definitions of PI, we used the one recommended by Johnsen in 1973 [7], *i.e.* intubation with mechanical ventilation ≥ one week, which is linked to huge likelihood of severe damage, specially, to the larynx and/or trachea.

Subjects were excluded from enrollment in case of 1) incomplete records, 2) refusal of participation, 3) inadequate follow-up (< 6 months), 4) planned head and neck surgery, 5) existing neurological and/or cognitive impairment, 6) Mallampati score class III or IV before PI, or 7) being tracheostomized after PI due to, for example, sputum obstruction, or inability to wean. Our primary observation showed that some SCOVIDS-PIs experienced TMJ pain. Hence, an in-house standard for CMD screening by the first author (P.P.) was set up.

The local institutional review board approved the project, and all subjects consented to their anonymous data use. The Helsinki Declaration's ethical guidelines and the STROBE statement were adhered throughout the study.

2.2. Study variables

The predictor variables were groups of parameters that could be associated with post-PI CMDs, which were grouped into the following categories: (1) demographic (age, gender), (2) dental (unilateral *vs.* bilateral loss of posterior teeth [molars] in one or both jaws *vs.* no molar loss), dentofacial skeletal relation [class I to III], underlying CMDs before SARS-CoV-2 infection [unknown/never noticed *vs.* yes *vs.* no] and regular dental checkups at least twice per year [yes/no], (3) anesthetic (PI < 3 week *vs.* ≥ 3 weeks [*i.e.* 1–20 days *vs.* ≥ 21 days]), and (4) laboratory groups (the highest serum C-reactive protein [CRP] during intensive medical care ≥ 40 mg/l [yes/no]).

Risk and perpetuating factors for CMDs include (1) dental factors, *e.g.* ≥ 5 missing teeth, posterior cross-bite, overjet and/or overbite greater than 5 mm, centric relation and/or maximum intercuspal sliding greater than 2 mm, edge-to-edge bite, sagittal relation class III, anterior open bite, (2) behavioral-cognitive factors (parafunctions), *e.g.* grinding, clenching, abnormal head posture, bruxism, (3) mechanical factors due to macrotrauma (*e.g.* whiplash-type injuries to the head and neck, OTI/PI), joint hyperlaxity and hypermobility, (4) hormonal factors, *i.e.* CMDs in women are 4 times more common than in men (probably due to the presence of estrogen receptors in women's TMJ, causing increased ligament laxity and susceptibility to painful stimuli via modulation of the limbic system by estrogen), and (5) emotional factors, *e.g.* depression and anxiety that induce muscle hyperactivity, fatigue and spasm, and subsequent dental occlusal disharmony, internal derangement, and degenerative arthritis. Conversely, chronic orofacial pain and headache can cause depression and anxiety [8]. Age and underlying CMDs within a pre-operative year were also found to be significantly associated with CMDs' symptoms lasting as long as 14 days post-OTI [2].

We added serum CRP to be a predictor variable because of inflammatory effects of SARS-CoV-2 on the musculoskeletal system via, for example, (1) angiotensin-converting enzyme 2 (ACE2) receptors used to enter host cells, including osteoblasts and osteoclasts, and blocks its receptor functions, including bone resorption, and maintaining bone structure, and (2) the nuclear factor κ B (RANK)/RANK-Ligand (RANKL) system and the tryptophan-kynurenine (Trp-Kyn) pathway activated by cytokine storm, causing inflammatory arthritis, muscle fibrosis, weakness, fatigue, and atrophy, sarcopenia, tendinopathy, and increased bone fragility [9–12]. The cut-off CRP ≥ 40 mg/l was used because of its association with disease severity at admission and mortality in COVID-19 patients [13].

The outcome variable was the presence of CMDs (yes/no) identified using the 2020 CMD screening protocol of the German Association for Functional Diagnostics and Therapy of the TMJ (DGFDT; available at: https://www.dgfdt.de/richtlinien_formulare; accessed June 30, 2022) (Fig. 1).

2.3. Data management and statistical analysis

Data entered a collection form in Microsoft Excel 2007 (Microsoft Inc., WA, USA). All analyses were performed using MedCalc® (MedCalc Software Ltd., Ostend, Belgium). Descriptive statistics were computed for each study variable, and bivariate analyses aimed to assess the association between the predictor and outcome variables. Variables associated with CMDs with $P \leq 0.15$ were used to generate a multiple logistic regression model to identify predictors statistically associated with CMDs. Significance was defined as $P \leq 0.05$ with two-sided hypothesis testing.

Spearman rho (r_s)'s ranked-order correlation coefficients would prove relationships between the candidate predictors and presence of CMDs or PI ≥ 3 weeks, and interpreted by the "rule of thumb": 0 to ±0.20 is negligible, ±0.21 to ±0.40 is weak, ±0.41 to ±0.60 is moderate, ±0.61 to ±0.80 is strong, and ±0.81 to ±1.00 is very strong [14]. We also calculated NNS, which equals 1 divided by absolute risk reduction, to indicate probability of benefiting (in terms of morbidity/mortality and up to a certain time point of follow-up) conditionally on being diagnosed [15,16].

Because we paid much attention to PI, the *post hoc* power based on this variable were computed using G Power 3 for Windows (HHU Düsseldorf, Düsseldorf, Germany) with an effect size of 0.5, an α error probability of 0.05, and a sample size of 176.

3. Results

176 subjects (21 with CMDs; 155 without CMDs; 53 women and 126 men) met the inclusion criteria; none was excluded. The mean age of the whole cohort was 59.2 ± 17.2 years (range, 27–89). In bivariate analyses, there were statistically significant associations between CMDs and five variables: age ≥ 59 years, bilateral molar loss in at least one jaw, skeletal class II (convex face), PI ≥ 3 weeks, and the highest serum CRP during intensive care ≥ 40 mg/l. Half of the

The German Association for Dental and Maxillofacial Health Care

DGFDT Deutsche Gesellschaft für Funktionsdiagnostik und -therapie Die Funktionsgesellschaft

The German Association for Functional Diagnosis and Therapy of the Temporomandibular Joint (TMJ)

CMD SCREENING (CMD BASIC DIAGNOSIS)

The German Association for Functional Diagnosis and Therapy of the TMJ (DGFDT)

..... Patient's Hospital No.	..... Last Name, First Name	..... Birthday	..... Examination Date

Patient's History (H)	Yes	No
H: Do you have **pain** at least one time a week? • in the temporal or facial area, • at the jaw or temporomandibular joint, • during mouth opening or chewing *and/or* • Difficulty or **limitation** of mouth opening		
Examination (E)	**Yes**	**No**
E: Pain of masticatory muscle(s)?		
E: Pain at the temporomandibular joint?		
E: Limitation of mouth opening?		
E: Malocclusion or occlusal disturbances?		
E: Temporomandibular joint sound?		

Fig. 1. The authors' translation of the 2020 CMD screening protocol of the German Association for Functional Diagnostics and Therapy of the TMJ (DGFDT; The original version in German is available at: https://www.dgfdt.de/richtlinien_formulare; accessed June 30, 2022).

samples were ≥ 59 years, confirming the likelihood of death in aging people (*i.e.* survivors were younger), and males were predominant (~70% of the cohort). Descriptive and bivariate comparisons between the variables are presented in Table 1.

Table 2 shows multiple logistic regression analysis, and r_s and NNS calculations, which included the five abovementioned parameters from the bivariate analysis. Although all r_s suggested possible relations between all parameters and CMDs, only bilateral molar loss (P = 0), convex face (P = .01), and high CRP (P = .01) were significant predictors of CMDs in SCOVIDS-PIs after controlling associated variables including age and intubation time span. Patients with bilateral molar loss had 12.6 greater odds (95% confidence interval [CI], 3.9 to 41.1) for developing CMD than those with no or only unilateral molar loss. Convex-face subjects (class II) were at 2.6-fold higher risk of CMDs (95%CI, 1.2 to 5.9) than those with normal or concave profile (class I or III). SCOVIDS-PIs with peak CRP ≥ 40 mg/l were 3.5 times more likely to have CMDs (95% CI, 1.0 to 12.1) than those with lower CRP.

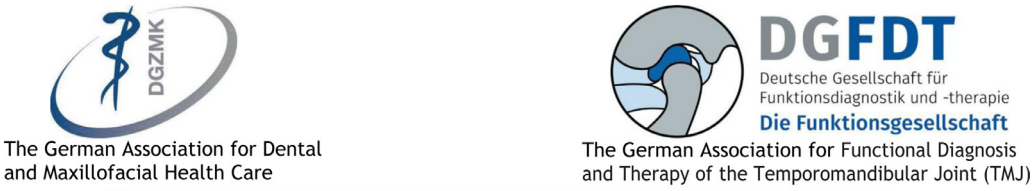

Fig. 1. Continued.

NNS calculations suggested that 10 events/patients with any form of CMDs would be averted per 16 to 43 (or ~1 per 2–4) screening for CMDs in "SCOVIDS-PI with one predictor factor". A combination of predictors increased the NNS values (range, 2 to 4.3), suggesting independence of each predictor. Among these risk factors, bilateral molar loss was the most potential indication of CMD screening (NNS = 1.6), while waiting for satisfying all of the three statistically significant predictors could not increase the merit of CMD screening (NNS = 4.3). In other words, only one predictor is enough to guide clinicians to screen CMDs in "SCOVIDS-PI ≥ 1 week" up to six post-PI months.

Table 3 demonstrates the relation of potential predictors and PI ≥ 3 weeks. In the adjusted model, variables associated with PI ≥ 3 weeks were age and tooth loss. The *post hoc* power was 89.5%, suggesting very high probability of accepting the alternative hypothesis and rejecting the null hypothesis, when the former is true.

Table 1
Binary analyses of all study variables *vs.* the presence of craniomandibular disorders (CMDs).

Characteristics	Overall	CMDs	Non-CMDs	*P*-value (RR; 95% CI)
Demographic				
Sample size	176 (100)	21 (11.9)	155 (88.1)	N/A
Age (range)	59.2 ± 17.2 (27–89)	71.0 ± 14.3 (35–89)	57.6 ± 17 (27–89)	**.0007 (N/A; 5.82 to 21.16)**
Age ≥ 59 years[†]	89 (50.6)	16 (76.2)	73 (47.1)	**.02 (3.13; 1.2 to 8.17)**
Female gender	53 (30.1)	8 (38.1)	45 (29.0)	.44 (0.87; 0.61 to 1.24)
Dental				
Loss of posterior teeth				**< 0.0001 (N/A)**
No	99 (56.3)	2 (9.5)	97 (62.6)	
Unilateral	51 (29)	4 (19.0)	47 (30.3)	
Bilateral	26 (14.8)	15 (71.4)	11 (7.1)	
Adjusted: bilateral *vs.* non-bilateral				**< 0.0001 (10.1; 5.36 to 18.91)**
Dentofacial skeletal class				**< 0.0001 (N/A)**
Class I (normal)	101 (57.4)	3 (14.3)	98 (63.2)	
Class II (convex face)	39 (22.2)	13 (61.9)	26 (16.8)	
Class III (concave face)	36 (20.5)	5 (23.8)	31 (20)	
Adjusted: class II *vs.* Non-class II				**< 0.0001 (3.69; 2.27 to 6)**
Self-reporting CMDs before COVID-19 infection				
Unknown (never noticed)	33 (18.8)	6 (28.6)	27 (17.4)	.33 (N/A)
Yes (with underlying CMDs)	26 (14.8)	4 (19.0)	22 (14.2)	
No (without underling CMDs)	117 (66.5)	11 (52.4)	106 (68.4)	
Adjusted: yes *vs.* no (excluding unknown/never noticed)				.35 (1.55; 0.62 to 3.9)
History of biannual dental check-ups				
Yes	116 (65.9)	12 (57.1)	104 (67.1)	.25 (0.8; 0.54 to 1.17)
No	60 (34.1)	9 (42.9)	51 (32.9)	
Anesthetic				
Intubation				
7–20 days	77 (43.8)	3 (14.3)	74 (47.7)	**< 0.0001 (1.64; 1.3 to 2.07)**
≥ 21 days	99 (56.3)	18 (85.7)	81 (52.3)	
Laboratory				
CRP ≥ 40 mg/l	73 (41.5)	14 (66.7)	59 (38.1)	**.0025 (1.75; 1.22 to 2.52)**

Note: [†] median of patient's age; RR – relative risk; 95% CI – 95% confidence interval; N/A – not applicable.
Continuous data are listed as mean ± SD, and categorical data are presented as number (percentage). Statistically significant *P*-values are indicated in **bold** typeface.

Table 2
Summary of the multiple logistic regression analysis, Spearman's rho (r_s), and number needed to screen (NNS) calculations.

Variables	Estimate	SE	*P*-value($OR_{adj.}$;95% CI)	r_s(P-value [2-tailed])			NNS		
The presence of CMDs[†]	−0.106	.042	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Age ≥ 59 years	−0.071	.048	.14 (0.28;.047 to 1.65)	**.189[a] (0.012)**	3.4				
Bilateral posterior tooth loss	.229	.033	**0 (12.64;**3.89 to 41.12)	**.462[b] (0)**	1.6	* 2.4	* 2		* 4.3
Skeletal class II (convex face)	.066	.025	**.011 (2.64; 1.18 to 5.89)**	**.256[c] (0.0006)**	2.2	*		* 3.8	*
Intubation ≥ 3 weeks	.072	.043	.095 (2.76;.61 to 12.51)	**.215[c] (0.004)**	3				
CRP ≥ 40 mg/l	.109	.041	**.01 (3.48;1.0 to 12.08)**	**.188[a] (0.012)**	3.5		*	*	*

Note: SE – standard error; $OR_{adj.}$ – adjusted odds ratio; 95% CI – 95% confidence interval; CMDs – craniomandibular disorders.
[†] – constant/intercept; N/A – not applicable.
[a] – no or negligible relationship.
[b] – strong relationship.
[c] – weak relationship; * – a combination of significant predictors for NNS calculation (completely black boxes are excluded). Statistically significant *P*-values of the multiple logistic regression analysis and Spearman's rho calculation are indicated in **bold** typeface.

Table 3
Secondary outcome analysis on factors associated with intubation ≥ 3 weeks using the multiple logistic regression analysis and Spearman's rho calculation.

Variables	Estimate	SE	*P*-value($OR_{adj.}$; 95% CI)	r_s(P-value [2-tailed])
Intubation ≥ 3 weeks[†]	.43	.066	N/A	N/A
Age ≥ 59 years	.167	.084	**.049 (2.0; 0.99 to 4.08)**	**.262[a] (0.0004)**
Bilateral posterior tooth loss	.116	.058	**.045 (1.71; 1.02 to 2.88)**	**.237[a] (0.0015)**
Skeletal class II (convex face)	.011	.045	.81 (1.06; 0.71 to 1.56)	.082[b] (0.28)
CRP ≥ 40 mg/l	−0.055	.074	.46 (0.79; 0.416 to 1.5)	−0.058[b] (0.447)

Note: SE – standard error; $OR_{adj.}$ – adjusted odds ratio; 95% CI – 95% confidence interval; r_s = Spearman's rho.
[†] – constant/intercept; N/A – not applicable.
[a] – weak relationship.
[b] – no or negligible relationship. Statistically significant *P*-values of the multiple logistic regression analysis and Spearman's rho calculation are indicated in **bold** typeface.

4. Discussion

Tracheostomy is often required in critically-ill mechanical ventilated patients (MVPs) without COVID-19. However, there remain many more doubts than certainties whether COVID-19 MVPs should apt to early tracheostomy (before day 10) instead of PI. A recent prospective study in 152 hospitals across 16 European countries (n = 1740) did not find the difference in 3-month mortality in MVPs aged ≥ 70 years after early *vs.* late tracheostomy (with PI) [17]. The results of a meta-narrative review, nonetheless, repudiated the benefit of early tracheostomy in COVID-19 MVPs (*i.e.* no significant effect on mortality, while high transmissibility risk due to high viral load), and ICU length of stay was shorter, if the MVPs remained intubated [18]. From these findings, it can thus be assumed that early tracheostomy suits COVID-19 MVPs aged ≥ 70 years only (*i.e.* mortality risks appear unchanged), while PIs in younger patients may be tolerated for 14–28 days [18] (in spite of higher likelihood of developing CMDs [2–6]).

The American Society of Anesthesiologists launched its current practice guidelines for difficult airway management in January 2022. It recommended that airway assessment, if the patient's difficult airway is known or suspected, must include measurement of facial and jaw features, *i.e.* mouth opening, ability to prognath, head/neck mobility, prominent incisors, and an upper lip bite test to reduce the risks of dental and TMJ injuries during OTI [19]. The mechanism of post-OTI CMDs, however, is unclear and often unnoticed until patients are awake and subjectively aware of symptoms afterwards, and may cause litigation [20].

Albeit remitting, self-limiting or fluctuating over time in most cases, untreated CMDs can produce chronic facial pain or headache, jaw malfunctions and/or deformity. Thus, there has been an attempt to identify the predictor of CMDs in MVPs with PI. The pre-OTI ability to open the mouth is objectively evaluated by the Mallampati score; however, this score is not a good predictor of post-OTI CMDs. The Mallampati score, despite a crude measure of reduced mandibular movement, is primarily a size assessment of the tongue in relation to the oropharynx, *i.e.* ability to visualize the oropharyngeal structures [2].

This study sought to identify potential predictor(s) of CMDs in SCOVIDS-PI up to six months post PI. Our null hypothesis was that variables selected in this study would not have a statistically significant effect on CMDs in SCOVIDS-PIs. The results of the present study refuted this hypothesis. Bilateral tooth loss, convex face, and high CRP provoked 12.6-, 2.6-, and 3.5-fold increased likelihoods of developing CMDs in SCOVIDS-PIs during six post-PI months, regardless of age, gender, underlying CMDs, or dental checkups. Relative to patients with no or unilateral molar loss, those with bilateral posterior tooth loss had a 71% increased likelihood of PI ≥ 3 weeks, and after adjusting dental/dentofacial skeletal status and peak CRP, patients aged ≥ 59 years were 2 times more likely to undergo PI ≥ 3 weeks than their younger counterpart. These findings support evidence from a US COVID-19 study (n = 486) that MVPs aged > 65 years were often on PI, and > 70% of hospitalized patients were intubated for ≥ 7 days [21].

Contrary to ours, a recent Brazilian study (n = 71; case-to-control = 1:1.5) rejected the differences in myogenic CMDs between ICU patients with *vs.* without OTI [3]. However, its *post hoc* power was only 8%, suggesting that the sample size is too small to be able to escape from type II error. Our findings are consistent with others that onset or progression of CMDs was associated with OTI [2,20,22,23], *i.e.* one in every 10 patients suffers from CMDs, such as pain during jaw movement, after non-difficult OTI for 7–14 postoperative days [2].

In the literature, three important factors, amid previous CMDs and skeletal class II, predisposing post-OTI patients to CMDs include (1) poor TMJ capsule integrity, (2) weak articular eminence morphology, and (3) muscle hypotonicity due to, for example, sedative agents, or muscle relaxants [20,22]. Although evidence-based data excluded the relationship between malocclusion and CMDs [24,25], we found the causal effect of tooth loss and/or skeletal malposition on post-PI CMDs. Edentulism often exerts substantial craniofacial morphological changes. Loss of bilateral molars in one or both jaws (*i.e.* no occlusal support) significantly shortens the posterior facial height, adapting the mandible to a new functional (protrusive) position for masticatiory performance, and TMJ tenderness via repetitive jaw protrusion [26]. Furthermore, there is evidence that apart from senile changes, autoimmune rheumatologic diseases, such as Sjögren's syndrome, increase susceptibility to TMJ arthritis and dislocation [27]. In subjects with at least one of these risk factor, trauma to the TMJ during intubation (from wide mouth opening and/or aggressive force) can escalate the risks of hematoma and subsequent intra-articular adhesion (because of high vascularity of the retroarticular tissue), disk displacement, and permanently aggravate TMJ laxity [20,22].

Concerning the facial form, approximately one-third of skeletal class II patients have myofascial pain, and these patients with myofascial pain have more risks of TMJ disk displacement, pain, depression, and polymorphisms of dopamine receptors *DRD2* (*rs6275* and *re6276*, indicating pain-related depression) [28]. Meta-analyses pointed out that class II malocclusion with a retrognathic mandible as well as hypodivergent faces with a steep dental occlusal plane were risk factors for degenerative changes of the TMJ [29,30]. After functional mandibular advancement with orthodontic appliances, CMD symptoms often disappear [31]. This also accords with our observations, which showed that SCOVIDS-PIs with skeletal class II were prone to post-PI CMDs.

There have been several investigations into associations between oral conditions (*e.g.* periodontal diseases, dental pulp gangrene, oral fungal infection, and jaw fractures) and increased CRP. It is therefore possible that high CRP results from CMDs. Prospective studies by Pihut et al. [32] (n = 72) and Park and Chung [33] (n = 40 females), nevertheless, found no relationship between this acute phase protein and painful CMDs. We can thus infer that increased CRP in our cohort represents a systemic inflammatory reaction due to COVID-19 rather than due to CMDs. In other words, CMDs in COVID-19 may be a systemic immune-related manifestation. Severe COVID-19 myalgia with creatine kinase levels >10,000 U/l (with/without renal failure) suggest myositis and/or rhabdomyolysis (frequency range, 1%–74%). Albeit multifactorial, immune-related muscular damage in COVID-19 patients, such as critical illness myopathy and superimposed steroid myopathy, is linked to critical illness and long ICU admission. Some patients may experience a direct cytolytic viral effect or damage related to hypercytokinemia, causing necrotizing autoimmune myopathy with acute, severe muscle weakness. Moreover, ~36% of COVID-19 patients have diverse arthritis patterns, *e.g.* symmetric polyarthritis (resembling rheumatoid arthritis), oligoarticular arthritis with skin lesions (resembling psoriatic arthritis) or axial enthesitis (resembling spondyloarthritis) [34]. We refer interested readers to our review on head and neck conditions in COVID-19 [35], and our research series regarding the effects of COVID-19 on oral-craniomaxillofacial surgery [36–39].

The strengths of this study include (1) a large generalizable sample and age range, and comparable gender distribution, underlying CMDs and dental checkups between two groups, (2) inclusion of all eligible SCOVIDS-PIs in a "pooled" ICU unit in a German "hot-spot area", (3) CMD screening by one assessor (P.P.) only, and (4) multivariate and NSS calculations. In sharp contrast, we concede the limitation that it was a retrospective, single-institution study. Some data were absent, that is, not recorded in all patients' charts, such as the Mallampati score so that we cannot conclude whether or not this score can be used to predict the CMD in this study. CMD frequency may also be overestimated because of no pre-ICU CMD examination. Moreover, data gathered by the DGFDT's CMD screening protocol

may be false positive (*e.g.* non-pathologic TMJ sounds), or false negative (*e.g.* pain and tenderness of medial and lateral pterygoid muscles are not investigated and included in the DGFDT-based "basic diagnosis"). In this study, radiologic investigations were not performed. Hence, osseous changes are not known. Longer-term dental follow-up among post-ICU patients is uncommon, and in this study, unstudied. The retrospective nature of the study limits the ability to control for bias or confounders. There is, therefore, abundant room for further researches in prospective, multi-institutional settings with a larger cohort.

5. Conclusions

This study was the first look for identifying predictors of CMDs in SCOVIDS-PIs up to six post-PI months. Our findings highlight three important predictors: (1) bilateral tooth loss, (2) skeletal class II (convex face), or (3) peak CRP during ICU stay ≥ 40 mg/l, whose MVPs should undergo CMD screening, regardless of complaint, age, gender, previous CMDs or dental checkups. The benefit-risk analysis favors post-PI CMD screening, *i.e.* screening of 2 to 4 SCOVIDS-PIs could find one CMD patients needed to be treated during the first 6 post-PI months.

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Ethical approval and consent to participate

The local institutional review board approved the project, and all subjects consented to their anonymous data use. The Helsinki Declaration and the STROBE statement were adhered.

Consent for publication

All authors reviewed and approved the final version of the manuscript.

Disclosure of potential conflicts of interest/competing interests

All of the authors indicate full freedom of investigation and manuscript preparation without potential conflict of interest as regards this study.

Availability of data and material

Deidentified individual participant data are not available. The datasets generated and analysed during this study are available from the first author (P.P.) upon reasonable request.

CRediT authorship contribution statement

Poramate Pitak-Arnnop: Conceptualization, Visualization, Funding acquisition, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Chatpong Tangmanee:** Conceptualization, Visualization, Funding acquisition, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Wantanee Mutirangura:** Conceptualization, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Benjamas Apipan:** Conceptualization, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Prim Auychai:** Conceptualization, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Jean-Paul Meningaud:** Conceptualization, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Andreas Neff:** Conceptualization, Formal analysis, Methodology, Writing – original draft, Writing – review & editing.

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