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Asymptomatic or mildly symptomatic COVID-19 patients with craniomaxillofacial injuries have an increased risk of surgical site infection

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Abstract

The aim of this paper was to evaluate the association between 'asymptomatic or mildly symptomatic' severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (AS/MS-COVID) and surgical site infection (SSI) after repair of craniomaxillofacial injury (CMFI). Using a case-control study design with a match ratio of 1:4, we enrolled a cohort of AS/MS-COVID cases with immediately treated CMFI during a one-year period. The main predictor variable was SARS-CoV-2 infection (yes/no), and the outcome of interest was SSI (yes/no). The other variables were demographic, clinical, and operative. Appropriate statistics were computed, and $p<0.05$ was considered statistically significant. The study group comprised 257 cases (28.8% female; 13.2% aged ≥ 60 years; 10.5% with fractures; 39.7% with involvement of nasal/oral/orbital tissue [viral reservoir organs, VROs]; 81.3% with blunt trauma; 19.1% developed an SSI [vs 6.8% in the control group]) with a mean (SD) age of 39.8 (16.6) years (range 19–87). There was a significant relation between SARS-CoV-2 infection and SSI events ($p<0.0001$; odds ratio 3.22; 95% confidence interval 2.17 to 4.78). On subgroup analysis, SSIs significantly increased with age ≥ 60 years, presence and treatment of fracture, contact with VROs, and prolonged antibiotic use (PAU). However, multivariate logistic regression analysis confirmed a positive effect only from old age, contact with VROs, and PAU (relative risk = 1.56, 2.52, and 2.03, respectively; $r = 0.49$; $p = 0.0001$). There was a significant 2.8-fold increase in SSIs among AS/MS-COVID cases, especially in those aged ≥ 60 years, or those with injuries to VROs, or both, who therefore required PAU.
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Keywords: SAS-CoV-2; COVID-19; Head and neck injury; Surgical site infection

Introduction

Elective surgical procedures have often been postponed or cancelled during the coronavirus disease 2019 (COVID-19) pandemic (as recommended by the AO CMF authors[1]) because they may be at high risk of viral transmission.

Microvascular alterations due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were found to cause surgical site infections (SSIs) at both donor and recipient sites in free fibular flap reconstruction.[2] Our recent study nevertheless demonstrated the absence of nosocomial SARS-CoV-2 infection among hospital personnel in contact with asymptomatic COVID-19 patients undergoing midfacial fracture repair,[1] suggesting that craniomaxillofacial injury (CMFI) care in asymptomatic or mildly symptomatic COVID-19 patients (AS/MS-COVID) could be safe. More-

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over, several studies have rejected the association between SARS-CoV-2 infection and SSI after hand surgery,[3] caesarean births,[4] and appendectomy.[5]

To the best of our knowledge, there is currently inadequate scientific evidence through well controlled epidemiological studies that explore the association between SSI events after CMFI treatment in COVID-19 patients. The aim of this study therefore was to assess the risk that AS/MS-COVID poses for the development of SSI in patients undergoing CMFI repair. This patient group was our research interest because they are the majority of COVID-19 patients in Germany (67%[6]) who may visit emergency departments (and could be treated without a diagnosis of SARS-CoV-2 infection). We hypothesised that the presence of AS/MS-COVID significantly increases the risk of SSI after CMFI surgery. Our specific purposes were first to identify a cohort of AS/MS-COVID patients with CMFI and estimate SSIs, secondly to assess additional risk factors for SSIs, and finally to construct a clinically relevant predictive model of disease (that is, SSI in relation to the presence of AS/MS-COVID).

Material and methods

Study design and sample description

The investigators designed and implemented a retrospective case-control, chart-review study, which was approved by the institutional review board. The ethical principles of the declaration of Helsinki[7] and the STROBE statement[8] were followed throughout the study.

Eligible cases had to meet five conditions: $\geq$ 18 years of age; SARS-CoV-2 infection tested twice as reported by our previous work;[1] American Society of Anesthesiologists (ASA) physical status classification system I or II with no conditions that could impair wound healing and/or increase the risk of an SSI, such as diabetes mellitus (DM);[9] mildly symptomatic (mild flu-like symptoms such as a sore throat, runny nose, loss of taste and/or smell, or diarrhoea)[6] or asymptomatic COVID-19; and immediate CMFI treatment during a one-year period in a German level I trauma centre of a regional hospital group comprising seven hospitals in six 'hot-spot' locations (>65,000 confirmed cases during the study period). The term 'immediate treatment' refers to appropriate patient care on arrival at hospital (for example, simple wound closure directly in the emergency department) and the first 24 hours of hospital stay (for example, facial fracture repair that may be postponed due to operating room capacity).[10,11] We identified the cases via the International Classification of Disease (ICD-10) diagnostic codes and Operation and Procedure Classification System (OPS) codes within the front-end anonym electronic medical records of the hospital's database. A list of the ICD and OPS codes used to identify potential cases is summarised in Table 1.

Subjects were excluded if CMFI surgery was unnecessary (such as closed, non-displaced, isolated nasal fractures), if COVID-19 symptoms were moderate to severe (for example, high fever, coughing, pneumonia, or requiring intensive medical care),[6] and if treatment was delayed ($\geq$ 14 days post-trauma) and may have caused more complications.[10,11]

Based on the hospital's database in a 10-year interval before COVID, four CMFI control cases were randomly recruited for each included case, and matched by gender, age ($\pm$ 5 years), injury, and treatment type. We used a control-to-case ratio of 4:1 to increase the statistical power of the study; ratios greater than 4:1 have little additional impact on power.[12]

Study variables

The primary predictor variable was SARS-CoV-2 infection (yes/no). The main outcome of interest was SSI (yes/no), defined by the US Centers for Disease Control and Prevention (CDC) as an infection related to an operative procedure that occurs at or near the surgical incision (or traumatic open wound) within 30 days of the procedure (including trauma surgery), or within 90 days if prosthetic material is implanted.[13] All the 'cases' were postoperatively admitted to an isolation room for $\geq$ 14 days from diagnosis or first symptom until an absence of COVID-19 symptoms for $\geq$ 48 hours, and two negative COVID-19 tests were confirmed irrespective of treatments received, as recommended by the German Robert Koch Institute (RKI) for Disease Control and Prevention.[14]

The other variables were demographic, clinical, and operative. The demographic variables were gender (female/male) and age (adjusted into binary according to an old age cut-off value: 18–59 vs $\geq$ 60 years). The clinical variables were mechanism of injury (blunt vs sharp/penetrating trauma) and location (presence of facial fracture or soft-tissue wound; contact with nasal/oral/orbital tissue that was a viral reservoir and may have increased intensive viral dispersion[1,15] [yes/no]). The operative variables were treatment (fracture repair vs simple wound closure), prolonged antibiotic use (PAU) $\geq$ 72 hours (yes/no), and hospital stay (yes/no).

Data management and statistical analysis

Anonymous data were compiled using a data abstraction form and analysed by two software tools: MedCalc® (MedCalc Software Ltd) to estimate the risk of SSI after CMFI treatments, and G* Power 3 for Windows (Düsseldorf, Germany) for post hoc power analysis.[16] We calculated odds ratios (OR), p values, 95% confidence intervals (CI), and relative risks (RR) using multivariate logistic regression, which accounted for matching factors. The multivariate logistic regression function was employed to test each independent variable separately and calculate the crude risk of SSI for each specific factor. We selected variables that were signifi-

Table 1

A: International Classification of Disease (ICD-10) diagnostic code and B: Operation and Procedure Classification System (OPS) code used to identify potential subjects for the case group (available from: https://www.icd-code.de/).

ICD codes	Diagnosis
S02.0, S02.1, S02.2, S02.3, S02.4, S02.5, S02.6, S02.7, S02.8	Craniomaxillofacial fractures
S00.01, S00.21, S00.31, S00.41, S00.51	Craniofacial abrasion wounds
S00.04, S00.24, S00.34, S00.44, S00.54	Foreign bodies in craniofacial region
S00.05, S00.1, S00.35, S00.45, S00.55	Craniofacial bruising/contusion
T14.4	Multiple nerve injuries
T14.5	Multiple vascular injuries
T14.6	Muscular and fascial injuries
J34.8	Diseases of nose and paranasal sinuses, eg septal haematoma
T1.0, S01.0, S01.1, S01.2, S01.3, S01.4, S01.5, S01.7	Open wounds in craniofacial region
K13.1	Cheek and lip biting
H05.0	Acute inflammation of orbit
H01.9	Inflammation of eyelids
H10.2	Acute conjunctivitis
S05.0	Conjuntival injury and corneal abrasion
H02.0	Entropium
H02.1	Ektropium
H02.4	Eyelid ptosis
S05.1	Contusion of globes and orbital tissue
S03.0	Temporomandibular joint luxation

OPS codes	Treatments
5-760.13, 5-760.14, 5-760.23, 5-760.24, 5-760.43, 5-760.44, 5-760.63, 5-760.64	Lateral midfacial (zygomatic arch or complex) fracture repair
5-761.13, 5-761.14, 5-761.33, 5-761.34, 5-761.43, 5-761.44	Central midfacial (maxillary, naso-orbitoethmoidal) fracture repair
5-762.13, 5-762.14, 5-762.53, 5-762.54	Combined centrolateral midfacial fracture repair
5-092.2, 5-086. 5-086.1, 5-086.30	Post-traumatic oculoplastic procedures
5-764.13, 5-764.14, 5-764.23, 5-764.24, 5-764.3, 5-764.43, 5-764.44, 5-765.13, 5-765.14, 5-765.23, 5-765.24, 5-765.33, 5-765.34, 5-765.43, 5-765.44, 5-765.72, 5-765.73, 5-765.74	Mandibular fracture repair
5-766.0, 5-766.1, 5-766.2, 5-766.3, 5-766.4, 5-766.5, 5-167.0, 5-167.1, 5-167.2	Orbital fracture repair
5-168.x	Optic nerve decompression
5-164.0	Releasing of retrobulbar haematoma
5-767, 5-767.0, 5-767.1, 5-767.2, 5-767.3, 5-767.4	Frontal fracture repair
5-892.00, 5-892.04, 5-892.05, 5-892.1, 5-892.10, 5-892.14, 5-892.15	Haematoma releasing in head and neck region (other than for retrobulbar haematoma) with/without drainage
5-896.00, 5-896.04, 5-896.05, 5-896.10, 5-896.14, 5-896.15	Debridement of head and neck region
5-928.00, 5-928.01, 5-928.01, 5-928.02, 5-928.03, 5-928.04, 5-928.05, 5-928.0h	Simple wound closure of head and neck region
5-769.0, 5-769.1, 5-769.2, 5-769.3, 5-769.4, 5-769.5, 5-769.6	Dental occlusion control, placement or removal of intermaxillary fixation
5-056.0	Neurolysis/decompression of cranial nerve outside skull
5-774.7, 5-774.70, 5-774.71, 5-774.72, 5-774.8	Plastic reconstruction and augmentation of maxilla
5-779.0, 5-779.1	Reduction of temporomandibular joint luxation

cant at p < 0.05 for further multivariate logistic regression analyses.

Results

A total of 257 'case' patients and 1028 controls were included for analysis. Within the case group, there were 74 females, 34 subjects aged ≥ 60 years, 27 who had facial fractures that required immediate treatment for retrobulbar haematoma, or treatment as a part of polytrauma surgery (others underwent delayed treatment after recovery from COVID-19), 102 (39.7%) with CMFI in contact with nasal/oral/orbital tissue (viral reservoir organs, VROs), and 209 (81.3%) with blunt trauma. The mean (SD) age was 39.8 (16.6) years (range 19–87). A total of 49 (19.1%) cases

and 70 (6.8%) controls had an SSI (p = 0.0001; OR, 3.22; 95% CI, 2.17 to 4.78).

On subgroup analysis, age ≥ 60 years, presence and treatment of fracture, contact with VROs, and PAU were significant risk factors for development of an SSI (R > 1.0). The RR for gender, injury mechanism (blunt trauma) and hospital stay was close to 1.0, indicating no effect on outcome (probably chance findings) (Table 2).

Multivariate logistic regression analysis confirmed a positive effect only from old age, contact with VROs, and PAU (RR = 1.56, 2.52, and 2.03, respectively; r = 0.49; p = 0.0001). There were moderate positive correlations between SSI events in older AS/MS-COVID patients and VRO-contamination and PAU. Despite a technically positive and negative association arising from the presence and treat-

Table 2
Cohort characteristics grouped by surgical site infection (SSI), and bivariate and multivariate analyses.

Parameters	Total* (n = 1285)	SSI (n = 119)	Non-SSI (n = 1,166)	p value (OR; 95% CI)	RR
Demographic:					
Female	370 (28.8)	40 (10.8)	330 (89.2)	0.24 (1.28; 0.86 to 1.92)	1.25**
Males	915 (71.2)	79 (8.6)	836 (91.4)		
Females: case group	74 (5.8)	11 (14.9)	63 (85.1)	0.21 (1.61; 0.76 to 3.39)	1.52**
Females: control group	296 (23)	29 (9.8)	267 (90.2)		
Age ≥ 60 years	170 (13.2)	82 (48.2)	88 (51.8)	< 0.0001 (27.15; 17.4 to 42.36)	14.54**
Age < 60 years	1,115 (86.8)	37 (3.3)	1,078 (96.7)		
Age ≥ 60 years: case group	34 (2.6)	23 (67.6)	11 (32.4)	0.013 (2.73; 1.23 to 6.04)	1.56**
Age ≥ 60 years: control group	136 (10.6)	59 (43.4)	77 (56.6)		
Clinical:					
Sharp/penetrating trauma	240 (18.7)	22 (9.2)	218 (90.8)	1.0(0.99; 0.61 to 1.6)	0.99
Blunt trauma	1045 (81.3)	97 (9.3)	948 (90.7)		
Blunt trauma: case group	209 (16.3)	18 (8.6)	191 (91.4)	0.46(1.24; 0.72 to 2.15)	1.22**
Blunt trauma fracture: control group	836 (65.1)	59 (7.1)	777 (92.9)		
Presence of fracture	135 (10.5)	21 (15.6)	114 (84.4)	0.012(1.98; 1.19 to 3.29)	1.83**
Soft tissue injury only	1,150 (89.5)	98 (8.5)	1,052 (91.5)		
Presence of fracture: case group	27 (2.1)	12 (44.4)	15 (55.6)	< 0.0001 (8.8; 3.17 to 24.42)	5.33**
Presence of fracture: control group	108 (8.4)	9 (8.3)	99 (91.7)		
Contact with VROs	510 (39.7)	88 (17.3)	422 (82.7)	< 0.0001(5; 3.27 to 7.67)	4.31**
No contact with VROs	775 (60.3)	31 (4)	744 (96)		
Contact with VROs: case group	102 (7.9)	34 (33.3)	68 (66.7)	< 0.0001(3.28; 1.99 to 5.41)	2.52**
Contact with VROs: control group	408 (31.8)	54 (13.2)	354 (86,8)		
Operative:					
Fracture repair	135 (10.5)	21 (16.8)	114 (84.4)	0.012(1.98; 1.19 to 3.29)	1.83**
Simple wound closure	1,150 (89.5)	98 (8.5)	1,052 (91.5)		
Fracture repair: case group	27 (2.1)	12 (44.4)	15 (55.6)	< 0.0001(8.8; 3.17 to 24.42)	5.33**
Fracture repair: control group	108 (8.4)	9 (8.3)	99 (91.7)		
Prolonged antibiotic use	305 (23.7)	95 (31.1)	210 (68.9)	< 0.0001(18.02; 11.24 to 28.89)	12.72**
No prolonged antibiotic use	980 (76.3)	24 (2.4)	956 (97.6)		
Prolonged antibiotic use: case group	61 (4.7)	32 (52.5)	29 (47.5)	0.0001(3.17; 1.78 to 5.65)	2.03**
Prolonged antibiotic use: control group	244 (19)	63 (25.8)	181 (74.2)		
Hospital stay	418 (32.5)	76 (18.2)	342 (81.8)	< 0.0001(4.26; 2.87 to 6.32)	3.67**
No hospital stay	867 (67.5)	43 (5)	824 (95)		
Hospital stay: case group	257 (20)	49 (19.1)	208 (80.9)	0.6 (1.17; 0.7 to 1.96)	1.14**
Hospital stay: control group	161 (14.8)	27 (16.8)	134 (83.2)		
Overall (whole cohort):					
Case group	257 (20)	49 (19.1)	208 (80.9)	< 0.0001 (3.22; 2.17 to 4.78)	2.8**
Control group	1,028 (80)	70 (6.8)	958 (93.2)		

VRO – viral reservoir organ; OR – adjusted odds ratio; 95% CI – 95% confidence interval; RR – relative risk. Categorical data are presented as number (percentage).

* Percentages in this column were calculated by the total subjects (n = 1,285).

** Risk factors were determined by relative risk values (RR > 1.0).

Table 3
Multivariate logistic regression analysis of study variables.

Predictor variables	Estimate	Standard error	r^2	r	p value
Age ≥ 60 years	0.1875	0.104	N/A	N/A	N/A
Presence of fracture	0.125	0.2543	0.0076	0.0872	0.63
Contact with viral reservoir organ	0.4375	0.1238	0.3262	0.5711	0.0014
Fracture repair	-0.4375	0.2886	0.0001	-0.0091	0.14
Prolonged antibiotic use	0.5	0.131	0.2757	0.5251	0.0007
				r^2	0.5548
				r	0.4934
Overall p value					0.0001

SSI: surgical site infection; N/A: not applicable.

ment of fractures, the relations between SSI events in elderly patients with SARS-CoV-2 infection and these parameters were weak (Spearman's $r = 0.087$ and -0.009) (Table 3).

The post hoc power estimate was 99.9% with an effect size of 0.5 and $\alpha = 0.05$, suggesting nearly a 100% chance of our research results with their real effect.

Discussion

This study is novel in using a scientific method to assess SSI events after CMFI repair in AS/MS-COVID patients. We found that these patients were 2.8 times more likely to suffer from SSIs, when compared with non-COVID patients. Hence, COVID-19 patients, albeit asymptomatic or mildly symptomatic, aged ≥ 60 years, and those with an injury in contact with VROs, or both, require particular attention when they have a CMFI.

It has been well known since the first pandemic wave that older people are severely affected by acute respiratory distress syndrome (ARDS) and high death rates. Patients at this age are prone to infections (that is, SARS-CoV-2 infection and others such as SSIs) and non-communicable chronic diseases due to physiological changes, especially chronic pro-inflammatory state and decreased function of innate and acquired immunity. Also they often have frailty, sarcopenia, disability, cognitive decline, anxiety, depression, and so on, which promote negative progression of the disease.[17] In this study, we followed the United Nations' (UN) definition of older persons, which accepts a chronological age of 60 years as the cut-off value.[18] However, a systematic review by Córdova et al[17] revealed that an age of ≥ 80 years was consistent with progressive physiological changes and was clinically relevant. We therefore did a further analysis using this cut-off and found that AS/MS-COVID patients aged ≥ 80 years were nearly twice as likely to develop SSIs than those aged 60-79 years (11/11 [100%] vs 12/23 [52.2%]; p = 0.0058; 95% CI: 1.3 to 2.83; RR: 1.92). Because we included ASA I-II patients only, SSIs in older patients with comorbidities and/or moderate to severe COVID-19, could be much higher and necessitate further investigation.

SARS-CoV-2 has a broad affinity for angiotensin-converting enzyme 2 (ACE2) on cell surfaces for entering host cells. ACE/ACE2 balance disruption and activation of the renin-angiotensin-aldosterone system caused by SARS-CoV-2 lead to disease progression, especially in patients with comorbidities such as diabetes mellitus and cardiovascular disease.[19,20] The binding of SARS-CoV-2 to ACE2 increases levels of angiotensin II (Ang II), a potent vasoconstrictor and proinflammatory molecule that exerts oxidative stress, mitochondrial dysfunction, endothelial cell damage, hypercoagulation, and thrombosis (via free radical generation), and jeopardises proper neovascularisation for wound healing.[2] High levels of serum plasminogen activator inhibitor-1 (PAI-1) and D-dimers are consistent with microthrombi observed in COVID-19 patients' autopsies.[20] Clinically, Inouye et al[2] reported free flap failure in patients with SARS-CoV-2, and Talmor et al[21] described necrosis and fail-

ure of a pedicled nasoseptal flap due to SARS-CoV-2 infection. A systematic review by Chen et al[22] concluded that SARS-CoV-2 reduces the cure rate of feet in diabetic patients, and increases healing time, amputation, and mortality rates.

Our recently published meta-narrative review[15] and prospective study[1] highlighted the finding that not only the airway and oral cavity, but ocular surfaces (which could be infected via the nasolacrimal duct) are VROs that could host a high viral density causing local microvascular pathology and poor wound healing. CMFI involving VROs is therefore a prominent risk factor for an SSI, significantly higher than the risk in surgery without VRO-contact, such as hand surgery,[3] caesarean birth,[4] or appendectomy[5] (49/257 [19.1%] vs 20/556 [3.6%] vs 1/43 [2.3%] vs 4/58 [6.9%]; p < 0.00001). To reduce the size of the surgical access and viral splattering, minimally invasive techniques could be an alternative to surgery involving VROs,[1,15] for example, the endoscope-assisted retrocaruncular approach for medial orbital wall and naso-orbitoethmoidal fractures reported by Meningaud et al and Pitak-Arnnop et al.[23,24]

A recent systematic review by Pitak-Arnnop[25] has suggested that facial fracture and contaminated/clean-contaminated wound repair require antibiotics for up to three and five days, respectively, while clean facial wounds need no antibiotic prophylaxis. PAU is reasonable in AS/MS-COVID patients with SSIs. Inouye et al[2] found that SSIs in COVID-19 patients were intensified by secondary bacterial infections, which emerge from *Staphylococcus aureus* (75%), *Escherichia coli* (58.3%), *Klebsiella pneumonia* (41.6%), *Pseudomonas aeruginosa* (33.3%), and *Acinetobacter baumannii*, *Streptococcus pneumoniae,* and *Haemophilus influenzae* (25%).[26] These populations should therefore be recognised as high-risk, as they are SSI-prone via acquired immunocompromise, poor microcirculation, and infected surgical sites (if they involve VROs), and may benefit from human recombinant soluble ACE2 (hrsACE2).[2] In other words, PAU could be rational if rigorously selected AS/MS-COVID patients with CMFI are treated before COVID-19 cures.

The strengths of this study are related to the case-control design, wherein each 'case' patient had their matched controls, and the strict inclusion and exclusion criteria. Some limitations, however, merit consideration. First, while the design was retrospective case-cohort, the study was not randomised a priori. The decision to treat CMFI was made on the basis of operator, patient, and hospital factors. Moreover, it has been evidenced that there was an increase in wound dehiscence and SSIs on the mask-covered face (due to frictional trauma by a mask) after Mohs micrographic surgery and parotidectomy during the COVID-19 pandemic.[27,28] Because of its retrospective nature, the correlation between use of a mask and wound dehiscence and SSI in our cohort was not monitored and was beyond our study's scope. Another potential shortcoming is the inclusion of ASA I-II patients only, which is probably unrealistic. Older patients often have comorbidities, suggesting that this study's generalisability (external validity) is reduced, while internal valid-

ity is increased. Additionally, the analyses herein did not assess the effect of radiographic and laboratory changes due to SARS-CoV-2 infection on SSI events and their severity because of heterogeneous patient management protocols. The 'cases' might have different, albeit usually negative, radiographic and laboratory changes.[6,17] Lastly, it is unknown whether and how SARS-CoV-2 creates local tissue alterations and subsequent SSIs. Bench research should be performed to answer this unresolved question.

Conclusions

AS/MS-COVID patients with CMFI have a 2.8-fold increase in SSIs (especially elderly patients injured in contact with VROs) and require PAU. In other words, close surveillance of SSIs using appropriate measures, such as evaluating C-reactive protein (CRP), is recommended. The presence and treatment of facial fracture in this group elicit positive and negative, albeit weak, correlations with SSI events, respectively. All CMFI patients should therefore be preoperatively tested for SARS-CoV-2 infection until the pandemic ends. We refer interested readers to a triage protocol for this group during the COVID-19 pandemic proposed by Wunsch and Pitak-Arnnop,[29] and research series on CMF surgery in COVID-19 patients.[1,15,30,31]

Ethics statement/confirmation of patients' permission

Approved by the institutional review board. All patients consented that we can use their anonymous data for research.

Funding

Nil.

Availability of data and material

Deidentified individual participant data are not available. Based on the current patient data protection law in Germany, open access to the raw data is not allowed. The datasets generated and analysed during this study are available from the corresponding author upon reasonable request.

Authors' contributions

Conception and design: P.P., C.T., C.M., J-P.M., A.N.

Acquisition, analysis and interpretation of data: P.P., C.T., C.M.

Drafting and revising the work: : P.P., C.T., C.M., J-P.M., A.N.

Final approval of the work: : P.P., C.T., C.M., J-P.M., A.N.

Agreement to all aspects of the work: : P.P., C.T., C.M., J-P.M., A.N.

Conflict of interest

We have no conflicts of interest.

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