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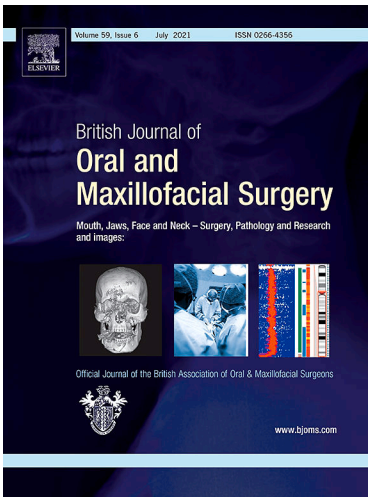

Asymptomatic or mildly symptomatic COVID-19 patients with craniomaxillofacial injuries have an increase risk of surgical site infection

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Full length Article:

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

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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.

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Full length Article:

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

Abstract

Purpose: 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 craniomaxillofacial injury (CMFI) repair.

Methods: Using a case-control study design with a match ratio of 1:4, we enrolled a cohort of AS/MS-COVID cases with CMFI immediately treated during a one-year interval. 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.

Results: The case group comprised 257 cases (28.8% females; 13.2% aged ≥ 60 years; 10.5% with fractures; 39.7% involved nasal/oral/orbital tissue [viral reservoir organs, VROs]; 81.3% blunt trauma; 19.1% developed SSI [*vs.* 6.8% in the control group]) with a mean age of 39.8 ± 16.6 years (range, 19-87). There was a significant relationship 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, contamination with VROs, and prolonged antibiotic use (PAU). However, multiple linear regression analysis confirmed the positive effect only from old age, contact with VROs, and PAU (relative risk = 1.56, 2.52, and 2.03; $r = 0.49$; $P = 0.0001$).

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Conclusion: There is a significant 2.8-fold increase in SSIs among AS/MS-COVID cases, especially those aged ≥ 60 years and/or injured to VROs, and thereby, require PAU.

Key words: SAS-CoV-2; COVID-19; head and neck injury; surgical site infection

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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 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. Moreover, several studies rejected the association between SARS-CoV-2 infection and surgical site infections (SSI) such as after hand surgery[3], caesarean births[4], or appendectomy[5].

To the best of our knowledge, there is currently inadequate scientific evidence through well controlled epidemiologic studies that explore the association between SSI events after CMFI treatments in COVID-19 patients. The aim of this study was to assess the risk that AS/MS-COVID poses in the development of SSI in patients undergoing CMFI repair. This patient group were our research interest because they are the majority of COVID-19 patients in Germany, i.e. 67%[6], and may visit emergency departments (or could be treated without the diagnosis of SARS-CoV-2 infection). We hypothesised that the presence of AS/MS-COVID increased the risk of SSI after CMFI surgery significantly. Our specific purposes were 1) to identify a cohort of AS/MS-COVID patients with CMFI and estimate SSIs, 2) to assess additional risk factors for SSIs, and 3) to construct a clinically relevant predictive model of disease (i.e. SSI in relation to the presence of AS/MS-COVID).

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Materials and Methods

1. 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 must meet five conditions: having 1) ≥ 18 years of age, 2) SARS-CoV-2 infection tested twice as reported by our previous work[1], 3) the American Society of Anesthesiologists (ASA) physical status classification system I or II without any conditions that could impair the wound healing and/or increase an SSI risk, such as diabetes mellitus (DM)[9], 4) mildly symptomatic (i.e. mild flu-like symptoms such as throat soreness, running nose, taste and/or smell loss, or diarrhoea)[6] or asymptomatic COVID-19, and 5) immediate CMFI treatments 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 at patient's hospital arrival (e.g. simple wound closure directly in the emergency department) until the first 24 hours of hospital stay (e.g. facial fracture repair which may be postponed due to operating room capacity).[10,11] We identified "cases" via 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 database. A list of ICD and OPS codes used to identify potential cases is summarised in *Table 1*.

Subjects were excluded if 1) CMFI surgery was unnecessary, such as closed, non-displaced, isolated nasal fractures, 2) COVID-19 symptoms were moderate to severe (e.g. high fever, coughing, pneumonia, or requiring intensive medical care)[6], and 3) treatment was delayed (≥ 14 days posttrauma), and may cause more complications.[10,11]

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

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2. 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 wounds) within 30 days of the procedure (including trauma surgery), or within 90 days if prosthetic materials is implanted at surgery.[13]

The other variables were demographic, clinical, and operative. The demographic variables were gender (female/male) and age (adjusted into binary according to the old age cut-off value: 18-59 *vs.* ≥ 60 years). The clinical variables were injury mechanism (blunt *vs.* sharp/penetrating trauma) and location (presence of facial fracture or soft-tissue wound; contact with nasal/oral/orbital tissue which is a viral reservoir and may increase intensive viral dispersion[1,14] [yes/no]). The operative variables were treatment (fracture repair *vs.* simple wound closure), prolonged antibiotic use (PAU) ≥ 72 hours (yes/no), and hospital stay (yes/no).

3. Data Management and Statistical Analysis

Anonymous data were compiled using a data abstraction form and analysed by two software tools: MedCalc® (Ostend, Belgium) to estimate the risk of SSI after CMFI treatments, and G Power 3 for Windows (Düsseldorf, Germany) for the *post hoc* power analysis. We calculated odds ratios (OR), *P* values, 95% confidence intervals (CI), and relative risks (RR) using conditional logistic regression, which accounted for matching factors. The conditional logistic regression function was employed to test each independent variable separately and calculate the crude risk of SSI for each specific factor. We selected those variables that were significant at $P < 0.05$ for further multivariate linear regression analyses.

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Results

There were 257 "case" patients and 1,028 controls were included for analysis. Within the "case" group, there were 74 females, 34 subjects aged ≥ 60 years, 27 with facial fractures requiring immediate treatments such as due to retrobulbar haematoma or as a part of polytrauma surgery [others underwent delayed treatment after COVID-19 healed], 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 age was 39.8 ± 16.6 years (range, 19-87). All of the 257 "cases" were postoperatively admitted to an isolated room for ≥ 14 days from the diagnosis or the first symptom until the absence of COVID-19 symptoms for ≥ 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.[15] 49 (or 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 of SSI development (R > 1.0). RR of gender, injury mechanism (i.e. blunt trauma) and hospital stay were close to 1.0, indicating no effect on the outcome (probably chance findings) (*Table 2*).

Multiple linear regression analysis confirmed the positive effect only from old age, contact with VROs, and PAU (RR = 1.56, 2.52, and 2.03; $r = 0.49$; $P = 0.0001$). There are moderate positive correlations between SSI events in older AS/MS-COVID patients and VRO-contamination and PAU. Despite technically positive and negative correlations arising from presence and treatments of fractures, the relationships between SSI events in elderly patients with SARS-CoV-2 infection and these parameters were weak ($r = 0.087$ 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 100% chance of our research results with their real effect.

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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 to non-COVID patients. Hence, COVID-19 patients, albeit asymptomatic or mildly symptomatic, aged ≥ 60 years and/or with injury in contact with VROs require particular attention, when they have CMFI.

It has been well known since the first pandemic wave that older people are severely affected through acute respiratory distress syndrome (ARDS) and high death rates. Patients at this age are prone to infections (i.e. SAS-COV-2 infection and others such as SSIs) and noncommunicable chronic diseases due to physiological changes especially chronic proinflammatory state and a decreased function of innate and acquired immunity. They often have frailty, sarcopenia, disability, cognitive decline, anxiety, depression, and so on, promoting negative progression of the disease.[16] In this study, we followed the United Nation (UN)'s definition of older persons, which accepts the chronological age of 60 years as the cut-off value.[17] However, a systematic review by Córdova *et al*.[16] revealed that age ≥ 80 years was consistent with progressive physiological changes and clinically relevant. We, therefore, did a further analysis using this cut-off and found that AS/MS-COVID patients aged ≥ 80 years were nearly 2 times more likely to develop SSIs than those aged 60-79 years (11/11 [or 100%] *vs*. 12/23 [or 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 investigations.

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 rennin-angiotensin-aldosterone system caused by SARS-CoV-2 lead to disease progression, especially in patients with comorbidities, such as DM and cardiovascular diseases.[18,19] The binding of SARS-CoV-2 to ACE2 increases levels of angiotensin II (Ang II), a potent vasoconstrictor and pro-inflammatory molecule which exerts oxidative stress, mitochondrial dysfunction, endothelial cell damage, hypercoagulation and thrombosis (via free radical generation), and jeopardise 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 patient autopsies.[19] Clinically, Inouye *et al.*[2] reported free flap failure in patients with SARS-CoV-2, and Talmor *et al*.[20] described pedicled nasoseptal flap necrosis and failure due to SARS-CoV-2 infection. A systematic review by Chen *et al*.[21] concluded that SARS-CoV-2 reduces a cure rate of diabetic feet, and increases healing time, amputation and mortality rates.

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Our recently published meta-narrative review[14] and prospective study[1] highlighted that not only the airway and oral cavity but ocular surfaces (which could be infected via the nasolacrimal duct) are VROs, and could host high viral density causing local microvascular pathology and poor wound healing. CMFI involving VROs are therefore a prominent risk factor for SSIs, which are significantly higher than surgery without VRO-contact, such as hand surgery[3], caesarean births[4], or appendectomy[5] (49/257 [19.1%] *vs.* 20/556 [3.6%] *vs.* 1/43 [2.3%] *vs.* 4/58 [6.9%]; $P < 0.00001$). Minimally invasive techniques could be an alternative for surgery involving VROs to reduce the surgical access size and viral splattering[1,14], e.g. Meningaud and Pitak-Arnnop's endoscope-assisted retrocaruncular approach for medial orbital wall and nasoorbitoethmoidal fractures.[22,23]

A recent systematic review by Pitak-Arnnop[24] suggested that facial fracture and contaminated/clean-contaminated wound repair require antibiotics up to 3 and 5 days, respectively, while clean facial wounds need no antibiotic prophylaxis. PAU is reasonable in the circumstances of AS/MS-COVID patients with SSI. 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%) as well as *Acinetobacter baumannii*, *Streptococcus pneumonia,* and *Haemophilus influenza* (25%).[25] These populations should, therefore, be recognised as high-risk and are SSI-prone via acquired immune compromise, poor microcirculation, and infected surgical sites (if involve VROs), and may benefit from human recombinant soluble ACE2 (*hrs*ACE2).[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. There are, however, some limitations associated with this study that 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 is 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.[26,27] Because of the retrospective nature, the correlation between the use of a mask and wound dehiscence and SSIs in our cohort was not monitored and is beyond our study's aim. Another potential shortcoming is an inclusion of ASA I-II patients only, which is probably unrealistic. Older patients often have comorbidities, suggesting that this study's generalisability (external validity) reduces, while internal validity increases. Additionally, the analyses herein did not assess the effect of radiographic and laboratory changes due to SARS-CoV-2 infection on SSI events and severity because of heterogeneous patient management protocols.

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The "cases" might have different, albeit usually negative, radiographic and laboratory changes.[6,16] 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.

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Conclusions

AS/MS-COVID patients with CMFI have a 2.8-fold increase in the SSI, especially elderly patients injured in contact with VROs, and require PAU. In other words, close surveillance of SSI using appropriate measures, such as C-reactive protein, is recommend in AS/MS-COVID patients with CMFI. The presence and treatments of facial fractures in this patient 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 CMFI patients during the COVID-19 pandemic proposed by Wunsch and Pitak-Arnnop.[28]

Conflict of Interest

Nil

Ethics statement/confirmation of patient permission

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

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Table 1 International Classification of Disease (ICD-10) diagnostic code and 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, e.g. 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 (i.e. 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 (i.e. maxillary, nasoorbitoethmoidal) fracture repair
5-762.13, 5-762.14, 5-762.53, 5-762.54	Combined centro-lateral midfacial fracture repair
5-092.2, 5-086. 5-086.1, 5-086.30	Posttraumatic 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 of head and neck region (other than for retrobulbar haematoma) with/without drainage

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5-896.00, 5-896.04, 5-896.05, 5-896.10, 5-896.14, 5-896.15	Débridement 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

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

Parameters	Total* (n = 1,285)	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	***1.25***
Males	915 (71.2)	79 (8.6)	836 (91.4)	(1.28; 0.86 to 1.92)	
Females: case group	74 (5.8)	11 (14.9)	63 (85.1)	0.21	***1.52***
Females: control group	296 (23)	29 (9.8)	267 (90.2)	(1.61; 0.76 to 3.39)	
Age ≥ 60 year	170 (13.2)	82 (48.2)	88 (51.8)	**< 0.0001**	***14.54***
Age < 60 years	1,115 (86.8)	37 (3.3)	1,078 (96.7)	**(27.15; 17.4 to 42.36)**	
Age ≥ 60 years: case group	34 (2.6)	23 (67.6)	11 (32.4)	**0.013**	***1.56***
Age ≥ 60 years: control group	136 (10.6)	59 (43.4)	77 (56.6)	**(2.73; 1.23 to 6.04)**	
Clinical					
Sharp/penetrating trauma	240 (18.7)	22 (9.2)	218 (90.8)	1.0	0.99
Blunt trauma	1045 (81.3)	97 (9.3)	948 (90.7)	(0.99; 0.61 to 1.6)	
Blunt trauma: case group	209 (16.3)	18 (8.6)	191 (91.4)	0.46	***1.22***
Blunt trauma fracture: control group	836 (65.1)	59 (7.1)	777 (92.9)	(1.24; 0.72 to 2.15)	
Presence of fracture	135 (10.5)	21 (15.6)	114 (84.4)	**0.012**	***1.83***
Soft tissue injury only	1,150 (89.5)	98 (8.5)	1,052 (91.5)	**(1.98; 1.19 to 3.29)**	
Presence of fracture: case group	27 (2.1)	12 (44.4)	15 (55.6)	**< 0.0001**	***5.33***
Presence of fracture: control group	108 (8.4)	9 (8.3)	99 (91.7)	**(8.8; 3.17 to 24.42)**	
Contact with VROs	510 (39.7)	88 (17.3)	422 (82.7)	**< 0.0001**	***4.31***
No contact with VROs	775 (60.3)	31 (4)	744 (96)	**(5; 3.27 to 7.67)**	
Contact with VROs: case group	102 (7.9)	34 (33.3)	68 (66.7)	**< 0.0001**	***2.52***
Contact with VROs: control group	408 (31.8)	54 (13.2)	354 (86,8)	**(3.28; 1.99 to 5.41)**	
Operative					
Fracture repair	135 (10.5)	21 (16.8)	114 (84.4)	**0.012**	***1.83***
Simple wound closure	1,150 (89.5)	98 (8.5)	1,052 (91.5)	**(1.98; 1.19 to 3.29)**	
Fracture repair: case group	27 (2.1)	12 (44.4)	15 (55.6)	**< 0.0001**	***5.33***
Fracture repair: control group	108 (8.4)	9 (8.3)	99 (91.7)	**(8.8; 3.17 to 24.42)**	
Prolonged antibiotic use	305 (23.7)	95 (31.1)	210 (68.9)	**< 0.0001**	***12.72***
No prolonged antibiotic use	980 (76.3)	24 (2.4)	956 (97.6)	**(18.02; 11.24 to 28.89)**	
Prolonged antibiotic use: case group	61 (4.7)	32 (52.5)	29 (47.5)	**0.0001**	***2.03***
Prolonged antibiotic use: control group	244 (19)	63 (25.8)	181 (74.2)	**(3.17; 1.78 to 5.65)**	
Hospital stay	418 (32.5)	76 (18.2)	342 (81.8)	**< 0.0001**	***3.67***
No hospital stay	867 (67.5)	43 (5)	824 (95)	**(4.26; 2.87 to 6.32)**	
Hospital stay: case group	257 (20)	49 (19.1)	208 (80.9)	0.6	***1.14***
Hospital stay: control group	161 (14.8)	27 (16.8)	134 (83.2)	(1.17; 0.7 to 1.96)	
Overall (whole cohort)					
Case group	257 (20)	49 (19.1)	208 (80.9)	**< 0.0001**	***2.8***
Control group	1,028 (80)	70 (6.8)	958 (93.2)	**(3.22; 2.17 to 4.78)**	

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Note: 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). Statistically significant *P*-values are indicated in **bold** typeface, and the risk factors were determined by relative risk values (RR > 1.0) and presented with ***bold and italic*** typeface.

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Table 3 Multivariate linear 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**

Note: SSI – surgical site infection; N/A – not applicable. Statistically significant *P*-values are indicated in **bold** typeface.

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