



Incidence of postoperative pneumonia in various surgical subspecialties: a retrospective study

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Abstract

Postoperative pneumonia (POP) can be defined as either hospital-acquired pneumonia (HAP, pneumonia developing 48–72 h after admission) or ventilator-associated pneumonia (VAP, pneumonia developing 48–72 h after endotracheal intubation) or within 30 days in postoperative patients. POP accounts for 2.7–3.4% of postoperative complications. Few studies have evaluated the incidence and the risk factors of POP. This study aimed to estimate the incidence of POP and identify the predictive factors of POP in King Abdul-Aziz University Hospital (KAUH), Jeddah, Saudi Arabia. This retrospective record review included all patients diagnosed with POP at KAUH between 2011 and 2021. Patients younger than 18 years of age and those diagnosed with congenital heart or lung disease were excluded from the study. Data were analyzed using the SPSS program version 26. Of the 2350 patients, 236 met the inclusion criteria. The mean age of patients was 58.12 ± 17.66 years; 82.6% had comorbidities. ENT (6.4%) and cardiothoracic surgeries associated with POP were the most common surgeries (4.2%). Comorbidities were found as an independent predictor of pneumonia among the studied patients ($P = 0.024$). The incidence of developing POP was (19.9%). Therefore, Physicians should be aware of POP. Especially when treating patients with comorbidities and patients on corticosteroids.

Keywords: postoperative pneumonia, surgery, risk factors

Introduction

Postoperative pneumonia (POP) can be defined as either hospital-acquired pneumonia (HAP, pneumonia developing 48–72 h after admission) or ventilator-associated pneumonia (VAP, pneumonia developing 48–72 h after endotracheal intubation) occurring in the post-surgical patient or that develops within 30 days after surgery. It is caused by various microorganisms and is characterized by cough, chest pain, and fever. It is a significant cause of morbidity and mortality worldwide^[1–4].

Pneumonia is a common postoperative complication, accounting for 2.7–3.4% of complications among surgical patients, and is the third most common nosocomial infection, with surgical patients accounting for 50%. It is considered the leading cause of mortality following hospital-acquired infection^[5,6].

Many risk factors are associated with POP, and they differ according to the surgical specialty. Cardiothoracic, diabetes

HIGHLIGHTS

- Incidence of POP at KAUH from 2011 to 2021 was 19.9%.
- The most common surgical subspecialty associated with POP is ENT (6.4%), following cardiothoracic surgery (4.3%).
- It was found that patients who developed POP had a significantly higher percentage of those who had any comorbidity and who were taking corticosteroids ($P < 0.05$).
- The predictive factor for developing POP was having comorbidities ($P = 0.024$).

mellitus, smoking, and chronic lung disease, while orthopedic determined independent risk factors to be male gender and long duration of tracheostomy. Patients who underwent transoral adenoidectomy were blood transfusions. General surgery, included the use of a nasogastric tube, blood transfusion, and diabetes^[1]. Ear, nose, and throat (ENT) appear that smoking history is the best predictor of postoperative pulmonary complications^[7].

The risk factors for POP vary by surgical specialty. Due to its significant impact and varying incidence among different specialties, it is important to thoroughly assess and gather data on this complication. This study aims to explore the incidence of POP and identify its risk factors in various surgical subspecialties at King Abdul-aziz University Hospital (KAUH) in Jeddah, Saudi Arabia.

Materials and methods

Study participants: A total of 2350 of all patients diagnosed with pneumonia between 2011 and 2021 were initially obtained from

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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the data system during the period 2021–2022, of which 236 met the inclusion criteria, including (1) aged older than 18 years; (2) All patients who have had any type of surgery in any specialized fields. Exclusion criteria: (1) Patients with missing date; (2) Patients with congenital heart and lung diseases because they are more susceptible than others to developing pneumonia, and we want to determine the independent factors affecting the acquisition of pneumonia.

Data collection: A predesigned checklist was Excel sheet was used to extract the data from the hospital's electronic database. The collected data included demographics (sex, age, BMI,

smoking status, comorbidities) and medications prior to the time of surgery. Surgical information such as surgical specialty, position at the time of surgery, surgical duration, surgical date, time of hospitalization, American Society of Anesthesiologist Score, estimated blood loss, saturation of peripheral oxygen (SPO₂), hemoglobin (Hb) concentration, blood pressure (BP), type of surgery (elective vs emergency), anesthetic technique, intraoperative complications, and the use of postoperative antibiotics. Postoperative data, such as days of hospitalization, the development of POP, culture results, radiographic findings, ICU admission and intubation, mortality, and the cause of mortality.

POP was defined as an infection of one or both lungs and diagnosed based on the following radiological criteria and clinical findings within 30 days after surgery. The radiological criteria included one definitive chest radiological examination (X-ray) demonstrating at least one of the following: new or progressive and persistent infiltrate, consolidation or opacity, and cavitation. The clinical findings had to meet at least one of the following criteria: fever ($>38^{\circ}\text{C}$) with no other recognized cause and leukopenia ($<4000/\text{mm}^3$) or leukocytosis ($\geq 12\,000/\text{mm}^3$).

Data analysis: Data were analyzed using the SPSS program version 26. To assess the association between the variables, the χ^2 was used for qualitative data that was expressed as numbers and percentages. Quantitative data were presented as mean and standard deviation (Mean \pm SD), where Mann–Whitney test was applied for non-parametric variables. Multivariate logistic regression analysis was done to assess the risk factors (independent predictors) of pneumonia among studied patients. The odds ratio was calculated at a CI of 95%. A *P* value of less than 0.05 was considered as statistically significant. The work has been reported in line with the STROCCS criteria^[8].

Table 1

Relationship between prevalence of POP and patients' demographics, BMI, smoking status, comorbidities, medications and position at the time of surgery (No.: 236).

Variable	Total	POP		χ^2	<i>P</i>
		No, N (%)	Yes, N (%)		
Age	58.12 \pm 17.66	57.52 \pm 17.4	60.51 \pm 18.68	1.24 ^a	0.214
BMI	28.36 \pm 13.7	29.05 \pm 14.94	25.5 \pm 5.59	1.7 ^a	0.089
Sex					
Female	140 (59.3)	115 (60.8)	25 (53.2)	0.91	0.339
Male	96 (40.7)	74 (39.2)	22 (46.8)		
Surgical specialty					
Cardiothoracic surgery	10 (4.2)	8 (4.2)	2 (4.3)	2.26	0.894
ENT surgery	9 (3.8)	6 (3.2)	3 (6.4)		
General surgery	9 (3.8)	8 (4.2)	1 (2.1)		
Neurosurgery	1 (0.4)	1 (0.5)	0 (0.0)		
OB.GYN	2 (0.8)	2 (1.1)	0 (0.0)		
Orthopedic surgery	4 (1.7)	3 (1.6)	1 (2.1)		
Current smoker	19 (8.1)	13 (6.9)	6 (12.8)	1.76	0.184
Comorbidities	195 (82.6)	150 (79.4)	45 (95.7)	7.03	0.008
DM	113 (47.9)	91 (48.1)	22 (46.8)	0.02	0.869
HTN	119 (50.4)	96 (50.8)	23 (48.9)	0.05	0.82
Dyslipidemia	46 (19.5)	35 (18.5)	11 (23.4)	0.57	0.449
CVD	46 (19.5)	39 (20.6)	7 (14.9)	0.79	0.374
Chronic pulmonary disease	14 (5.9)	10 (5.3)	4 (8.5)	0.69	0.403
Renal disease	17 (7.2)	14 (7.4)	3 (6.4)	0.05	0.808
Hypothyroidism	12 (5.1)	11 (5.8)	1 (2.1)	1.06	0.302
Other	58 (24.6)	43 (22.8)	15 (31.9)	1.7	0.192
Patient position					
Lithotomy	12 (5.1)	12 (6.3)	0	4.35	0.226
Prone	2 (0.8)	1 (0.5)	1 (2.1)		
Supine	210 (89)	167 (88.4)	43 (91.5)		
Other	12 (5.1)	9 (4.8)	3 (6.4)		
Medications at time of surgery	142 (60.2)	109 (57.7)	33 (70.2)	2.47	0.116
Corticosteroid	14 (5.9)	8 (4.2)	6 (12.8)	4.91	0.027
BB	17 (7.2)	12 (6.3)	5 (10.6)	1.03	0.309
Diuretic	14 (5.9)	12 (6.3)	2 (4.3)	0.29	0.587
ACEI	22 (9.3)	15 (7.9)	7 (14.9)	2.15	0.142
CCB	16 (6.8)	14 (7.4)	2 (4.3)	0.59	0.442
Acetyl salicylate acid	24 (10.2)	21 (11.1)	3 (6.4)	0.92	0.337
Statin	40 (16.9)	34 (18)	6 (12.8)	0.73	0.393
Antibiotic	27 (11.4)	20 (10.6)	7 (14.9)	0.69	0.406
Antifungal	2 (0.8)	2 (1.1)	0 (0.0)	0.5	0.479

ACEI, Angiotensin-converting enzyme inhibitors; BB, Beta blocker; CCB, Calcium channel blocker; CVD, Cardiovascular diseases; DM, diabetes mellitus; ENT, ear, nose, and throat; HTN, Hypertension; POP, postoperative pneumonia.

^aMann–Whitney test.

Results

Of the studied 236 patients, 47 (19.9%) suffered POP. Thus, the incidence was 199 per 1000 patients.

The mean age of patients was 58.12 ± 17.66 years, and their mean BMI was 28.36 ± 13.7 kg/m². Of them, 59.3% were females, and 3.8% were in the ENT or the general surgery specialty. Only 8.1% were current smokers, and 82.6% had comorbidities in the total study population, with hypertension (50.4%) and DM (47.9%) being the most common. Most of the patients (89%) had a supine position, and 60.3% were taking medications at the time of surgery, with antibiotics (11.4%) and acetylsalicylate acid (10.2%) being the most commonly taken medications. It was found that patients who developed POP had a significantly higher percentage of those who had any comorbidity and who were taking corticosteroids ($P < 0.05$). On the other hand, a non-significant relationship was found between the prevalence of pneumonia and patients' demographics, BMI, smoking status, or position at the time of surgery ($P \geq 0.05$). (Table 1) As for the surgical data, the mean estimated blood loss was 97.76 ± 7.1 ml, and the mean SpO₂ was 98.25 ± 2.73 . The mean Hb concentration was 10.7 ± 2 , and the mean systolic blood pressure and diastolic blood pressure were 129.06 ± 20.04 and 71.56 ± 14.67 , respectively. The mean surgical duration was 125.02 ± 112.89 min, and the mean hospital stay was 18.91 ± 40.78 days. Most of the patients (39.4%) had an II American Society of Anesthesiologist score, while 33.1% and 16.5% had III and IV scores, respectively. About 46% (46.2%) had a scheduled

Table 2
Relationship between prevalence of POP and surgical data, time of hospitalization and postoperative antibiotics (No.: 236).

Variable	Total	POP		χ^2	P
		No, N (%)	Yes, N (%)		
Estimated blood loss (ml)	97.76 ± 7.1	98.21 ± 2.92	95.97 ± 14.84	0.13 ^a	0.896
SpO ₂ (%)	98.25 ± 2.73	98.21 ± 2.92	98.43 ± 1.77	0.13 ^a	0.889
Hb concentration (g/dl)	10.7 ± 2	10.83 ± 2.02	10.19 ± 1.85	1.85 ^a	0.063
SBP	129.06 ± 20.04	130.12 ± 20.41	124.71 ± 18.09	1.51 ^a	0.131
DBP	71.56 ± 14.67	72.6 ± 14.03	67.44 ± 16.52	1.5 ^a	0.133
Surgical duration (min)	125.02 ± 112.89	127.27 ± 112.71	116.02 ± 114.38	1.08 ^a	0.277
Time of hospitalization (days)	18.91 ± 40.78	17.74 ± 34.45	23.55 ± 60.17	0.41 ^a	0.681
ASA Score					
I	26 (11)	18 (9.5)	8 (17)	5.59	0.133
II	93 (39.4)	77 (40.7)	16 (34)		
III	78 (33.1)	59 (31.2)	19 (40.4)		
IV	39 (16.5)	35 (18.5)	4 (8.5)		
Type of surgery					
Emergency	109 (46.2)	85 (45)	24 (51.1)	0.56	0.454
Scheduled	127 (53.8)	104 (55)	23 (48.9)		
Anesthetic technique					
General	156 (66.1)	126 (66.7)	30 (63.8)	0.31	0.856
Local	63 (26.7)	49 (25.7)	14 (29.8)		
Both	17 (7.2)	14 (7.4)	3 (6.4)		
Complications during surgery	7 (3)	6 (3.2)	1 (2.1)	0.14	0.701
Postoperative antibiotics					
Metronidazole	26 (11)	23 (12.2)	3 (6.4)	1.28	0.257
Penicillin	148 (62.7)	114 (60.3)	34 (72.3)	2.32	0.127
Cephalosporin	6 (2.5)	5 (2.6)	1 (2.1)	0.04	0.84
Ciprofloxacin	31 (13.1)	23 (12.2)	8 (17)	0.77	0.378
Cotrimoxazole	1 (0.4)	1 (0.5)	0	0.25	0.617
B-Lactamae inhibitor	23 (9.7)	12 (11.1)	2 (4.3)	2.01	0.156
Licomycin	12 (5.1)	11 (5.8)	1 (2.1)	1.06	0.302
Carbapenem	9 (3.8)	9 (4.8)	0	2.32	0.127
Glycylcycline	1 (0.4)	1 (0.5)	0	0.25	0.617

ASA, american society of anesthesiologist; DBP, Diastolic blood pressurre; Hb, hemoglobin; SPO₂, saturation of peripheral oxygen.

^aMann-Whitney test.

surgery, and 66.1% had general anesthesia. Only 3% had complications during surgery, and the most commonly taken postoperative antibiotic was Penicillin (62.7%). On the other hand, a non-significant relationship was found between the prevalence of pneumonia and surgical data, time of hospitalization, or postoperative antibiotics ($P \geq 0.05$). (Table 2)

About 14% (14.4%) of patients had positive culture findings, and the most had negative bacteria (8.9%). As for the radiology findings, 15.3% of patients had either opacification or Infiltration at a percentage of 15.3%. (Table 3)

About 16% (16.5) of patients underwent radiology; the most common finding was pleural effusion (23%). Almost one-third of patients (30.5%) had an ICU admission, and 24.2% had an ICU

Table 3
Positive culture and radiology findings of studies patients.

Variable	N (%)
Positive culture findings	34 (14.4)
Type of organism (Culture)	
Negative bacilli	21 (8.9)
Positive Cocci	8 (3.4)
Yeast cell	5 (2.1)
Mixed bacteria	3 (1.3)
Radiology findings	
Opacification	6 (15.3)
Infiltration	6 (15.3)
NA	17 (43.9)
pleural effusion	9 (23)
pleural effusion and infiltration	1 (2.5)

NA, not determined.

Table 4
Relationship between prevalence of POP and postoperative management data and (No.: 236).

Variable	Total	POP		χ^2	P
		No, N (%)	Yes, N (%)		
Underwent radiology	39 (16.5)	28 (14.8)	11 (23.4)	2.01	0.156
ICU admission	72 (30.5)	56 (29.6)	16 (34)	5.76	0.124
Intubation (ICU)	57 (24.2)	41 (21.7)	16 (34)	3.13	0.077
Mortality	65 (27.5)	40 (21.2)	25 (53.2)	19.34	< 0.001
Mortality cause (No.: 65)					
Cancer	4 (6.1)	4 (2.1)	0		
Cardiac arrest	9 (13.8)	6 (3.2)	3 (4.6)	58.04	< 0.001
COPD	1 (1.5)	1 (0.5)	0		
Hemorrhage	1 (1.5)	1 (0.5)	0		
Hypertension	1 (1.5)	1 (0.5)	0		
Metastasis	2 (3)	0	2 (4.3)		
NA	2 (3)	2 (1.1)	0		
obstructive sleep apnea	1 (1.5)	1 (0.5)	0		
Pneumonia	26 (40.6)	8 (4.2)	18 (38.3)		
Postoperative complications	5 (7.6)	4 (2.1)	1 (2.1)		
Sepsis	8 (12.3)	7 (3.7)	1 (2.1)		
Shock	4 (6.1)	4 (2.1)	0		
Stroke	1 (1.5)	1 (0.5)	0		

COPD, Chronic obstructive pulmonary disease; NA, not determined; POP, postoperative pneumonia.

intubation. Of the patients, 27.5% were deceased, and the most common cause was pneumonia (40.6%). It was found that the prevalence of the development of POP was significantly higher among patients having pulmonary infiltration and who died ($P < 0.05$). (Table 4)

Multivariate logistic regression analysis was done to assess the risk factors (independent predictors) of pneumonia among

Table 5
Multivariate logistic regression analysis of risk factors of pneumonia among studied patients.

Variable	B	Wald	P	Odds ratio (CI:95%)
Having any comorbidity	1.71	5.12	0.024	5.61 (1.36–22.17)
Using corticosteroid at time of surgery	1.09	3.34	0.104	0.67 (0.35–1.12)

studied patients. It was found that having any comorbidity (independent predictors) of pneumonia among studied patients (Table 5).

Discussion

Comorbidities and POP

Our study found that comorbidities, especially diabetes mellitus (DM), are significantly associated (POP). Diabetic patients are more prone to infections due to possible immune defects^[9]. DM was reported in four studies as one of the most common risk factors for POP^[10–13]. The most common risk factor for POP is diabetes after general, orthopedic, and spinal surgeries^[14].

A systemic review conducted by Vardakas *et al.*^[15] showed that DM is not a risk factor for the development of HAP, and they are not at an increased risk of developing VAP. POP is associated with poor long-term outcomes in patients with gastric cancer^[16]. Vera Urquiza *et al.*^[17] reported that hypertension is the independent risk factor of POP after cardiothoracic surgery. The overall incidence of POP was 3.11% in 57 201 surgical procedures in a previous study. Risk factors included hypertension, other comorbidities such as low BMI and craniotomy^[18].

Corticosteroids and POP

Prolonged corticosteroid use weakens the immune system, increasing infection risk such as septic shock^[19].

Our study revealed a significant correlation between pre-operative steroid use and the incidence of POP. Corticosteroid-treated patients experienced multiple perioperative complications, including pneumonia^[20]. In contrast, a 2020 study found no significant link between long-term corticosteroid use before surgery and the development of POP^[19]. There were no statistically significant differences in the incidence of postoperative respiratory complications between the perioperative Inhaled Corticosteroid treatment group and control group in another study^[21].

General surgery and POP

In this study, 9 (3.8%) patients developed POP after general surgery. Several retrospective studies have shown that the incidence of POP varies among patients who had undergone gastrectomy, pancreatoduodenectomy or distal pancreatectomy. Kiuchi *et al.*^[22] reported a 2.2% incidence of POP among patients who underwent gastrectomy, A study reported a 4.3% incidence among patients who underwent gastrectomy^[13]. Another study observed an incidence of 4.7% among patients who underwent gastrectomy^[23].

Cardiothoracic surgeries and POP

Most of our patients in this study underwent cardiothoracic surgeries of the surgical subspecialties, and only two developed POP. While, Strobel *et al.*^[24] found that 3.3% developed pneumonia Vera Urquiza and colleagues' prospective study reported an incidence of 14.6%^[15], and Poelaert *et al.*^[25]'s study reported an incidence of 32%. Miyata *et al.*^[26]'s study who underwent cardiovascular surgery reported an incidence of 9.8% of post-operative aspiration pneumonia. According to a concluded study, it is believed that cardiothoracic surgery is a prevalent cause of

POP, primarily due to associated risk factors like advanced age and chronic obstructive pulmonary disease^[27].

Orthopedic surgeries and POP

The incidence in our study was (1.7%). However, Song *et al.*^[28] reported that 14.4% of patients who underwent total knee arthroplasty experienced POP. Lv and colleagues conducted a retrospective study of patients who underwent hip-fracture surgery and found a 4.9% incidence of POP^[12]. Bohl *et al.*^[29] reviewed patients who underwent anterior cervical decompression and fusion and discovered a POP incidence of 0.45%. Another retrospective study by Bohl *et al.*^[30] examined patients who underwent posterior lumbar fusion and found a POP incidence of 0.59%. ENT surgeries and POP

ENT surgeries were the most common surgical subspecialty associated with POP development (6.4%). Li *et al.*^[31] studied patients who underwent tracheostomy and reported an incidence of 19.7% POP. Marda *et al.*^[32] reviewed patients who underwent odontoidectomy and posterior fixation, found a rate of 5.6% of POP. Damian *et al.*^[33] reviewed head and neck surgery and reported a POP incidence of 9.1%. We believe that the most common surgical subspecialties correlate with POP due to smoking history being the primary variable related to post-operative pulmonary problems, with evidence of increasing risk with increased exposure^[34].

Patient position and POP

Gastro-esophageal reflux (GER) can increase the risk of pneumonia in hospitalized patients due to aspiration. Limited mobility can exacerbate this risk^[18,35]. Our study found no correlation between patient position and pneumonia, which is consistent with Watanabe and colleagues study^[36]. However, a randomized trial showed that clinically suspected nosocomial pneumonia was less common in the semi-recumbent group than in the supine group^[35]. Another study indicated that the semi-recumbent position does not fully protect against GER and oropharyngeal colonization of gastric origin^[37].

Surgical duration and POP

A study found that longer operative times are related to an increased risk of postoperative pulmonary complications^[38]. The risk of complications also increased with each half-hour increase in operative time with 31.4% for those lasting more than 6 h^[39]. Another study identified longer procedures as a significant risk factor for POP, In patients of post-cardiac surgery and a correlation was found between longer operative times and overall hospital stays^[40].

Organisms causing POP

In our study, Gram-negative bacilli were the most commonly isolated microorganisms. However, a study of POP following cardiac surgery found that *Haemophilus influenzae* was the most common organism^[40]. Another study discovered that *Acinetobacter* species were the most frequently isolated organisms in cases of POP (44.4%)^[41]. In a study of patients who underwent esophagectomy, *Candida* was the most commonly found organism (19.4%)^[42].

ICU admission and POP

Our study found no significant association between POP and ICU admission. However, a study in India in 2013 showed a significant correlation between POP incidence and ICU stay^[41]. Another study found a significant correlation between lung resection and ICU admission, with a median ICU stay of 7 days^[43]. A study found that longer hospital stays and higher rates of ICU admissions were independent risk factors for pneumonia^[44]. Similarly, Damian *et al.*^[45] concluded that patients requiring longer ventilation support and frequent ICU admissions had a higher risk of POP.

Mortality and POP

POP continues to be a major cause of mortality in surgical settings. Determinants of survival in patients with POP have not yet been clearly defined^[46]. The mortality rate in our present study was 65; 18 were due to POP. In another study involving 103 patients, 16 died, of which 10 patients had POP^[47]. The mortality rate of patients who developed POP was 19%^[48]. In a study assessing risk factors for POP after cardiac surgery, (42.5%) death were observed in patients with POP. The POP rate observed in this study (3.1%) was within the low range of previously reported rates (2-9.7%)^[49]. A significant correlation between patients who underwent hip-fracture surgery and POP mortality^[50].

Limitations

The study has limitations as it was a single-center retrospective study with a small population, missing data, and restricted database access. For future research, we recommend prospective multicenter designs with a larger population and longer duration, investigating the specific types of surgery associated with POP in each surgical subspecialty.

Conclusions

This study aimed to determine the factors contributing to the occurrence of POP and identify potential predictors of KAUH. Of the 236 patients examined, 47 (19.9%) were diagnosed with POP, and the percentage of patients who had comorbidities and used preoperative corticosteroids was significantly higher among those who developed POP ($P < 0.05$). Additionally, the prevalence of POP was significantly higher in patients with pulmonary infiltration ($P < 0.05$). Our findings also suggest that comorbidities are a predictive factor for POP ($P = 0.024$). We determined the critical risk factors associated with POP and established a specific subpopulation of patients who are particularly susceptible to developing this condition. Physicians must remain aware of the potential for preventable nosocomial infections, especially when treating patients with comorbidities and administering corticosteroids.

Ethical approval

This study was conducted in accordance with the declaration of Helsinki and approved by the Institutional Review Board (IRB) of King AbdulAziz University Hospital (KAUH) (Reference No. 39-22) on 2 February 2022.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contribution

Conceptualization: F.A.T., M.A.; methodology: M.A., R.A.; software: F.A.T., M.A., R.A.; validation: F.A.T., and M.A., R.A.; formal analysis: F.A.T.; investigation: M.A.; resources: M.A., R.A.; data curation, M.A.; writing—original draft preparation: M.A., R.A., F.A.T.; writing—review and editing: M.A.; visualization: R.A.; supervision: F.A.T.; project administration: F.A.T., M.A., R.A. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest disclosure

The authors declare no conflicts of interest.

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Data availability statement

Data are not available due to patient's privacy.

Provenance and peer review

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