


# Predictors of Complications Occurrence Associated With Emergency Surgical Tracheotomy

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## Abstract

**Objective.** In emergency airway management, the occurrence of surgical tracheotomy complications is increased and may be fatal for the patient. However, the factors that play a role in complication occurrence and lead to lethal outcome are not known. The objective of this study was to determine predictors associated with the occurrence of complications and mortality after emergency surgical tracheostomy.

**Study Design.** Retrospective study with a systematic review of the literature.

**Setting.** Tertiary medical academic center.

**Subjects and Methods.** We included 402 adult patients who underwent emergency surgical tracheostomy under local anesthesia due to upper airway obstruction. Demographic, clinical, complication occurrence, and mortality data were collected. For statistical analysis, univariable and multivariable logistic regression methods were used.

**Results.** In multivariable analysis, significant positive predictors of complication occurrence were previously performed tracheotomy (odds ratio [OR] 3.67, 95% confidence interval [CI], 0.75–17.88), neck pathology (OR 2.05, 95% CI 1.1–1.77), and tracheotomy performed outside the operating room (OR 5.88, 95% CI, 1.58–20). General in-hospital mortality was 4%, but lethal outcome as a direct result of tracheotomy complications occurred in only 4 patients (1%) because of intraoperative and postoperative complications.

**Conclusion.** The existence of neck pathology and situations in which tracheotomy was performed outside the operating room in uncontrolled conditions were significant prognostic factors for complication occurrence. Tracheotomy-related mortality was greater in patients with intraoperative and early postoperative complications. Clinicians should be aware of the increased risk in specific cases, to prepare, prevent, or manage unwanted outcomes in further treatment and care.

## Keywords

emergency surgical tracheotomy, tracheostomy complication, tracheostomy-related mortality, predictors

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One important indication for emergency airway management by surgical tracheotomy and nasotracheal or orotracheal intubation is acute airway obstruction.<sup>1</sup> In these cases, emergency surgical tracheotomy is performed under local anesthesia on an awake patient, often under substandard conditions. Patients are at increased risk of hypoxia and cardiopulmonary arrest, and the speed and precision of the surgeon are of utmost importance.

Although the surgical procedure and indication for surgical tracheotomy are well established, complications and sequelae occur and can be fatal for the patient. Complications associated with surgical tracheostomy are classified according to the time of their occurrence as (1) intraoperative (occurring within the first 24 hours), (2) early postoperative complications (occurring during the first 14 days), and (3) late postoperative complications (occurring 14 days after tracheostomy).<sup>2,3</sup> The complication rate varies from 5% to 40%, and the mortality rate can be as high as 2% depending on the study.<sup>1,4</sup> In emergency situations, the occurrence of complications is increased 2- to 5-fold.<sup>5</sup> Possible causes of higher complication rates include a mixed population of patients with comorbidities requiring an emergency procedure without previous preparation, the experience of the team performing the procedure, and anatomical and pathological variations of the surgical field.

The objective of this study was to determine the predictors associated with the occurrence of complications and mortality after emergency surgical tracheostomy.

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## Materials and Methods

### Retrospective Review

The study was conducted on 402 adult patients ( $\geq 18$  years) who underwent emergency surgical tracheostomy under local anesthesia following upper airway obstruction. The data were obtained by retrospective review of the medical records of patients admitted to the Clinic for Otorhinolaryngology and Maxillofacial Surgery, Clinical Center of Serbia, Belgrade, during a 5-year period (from January 1, 2015, to January 31, 2020). The study was approved by the Ethics Committee of the Clinical Center of Serbia (227/V-1/14).

During the 5-year period researched in the study, 26 otolaryngology–head and neck (ORL-H&N) surgeons made the decision as to whether emergency tracheotomy was indicated. The decision was made individually for every patient after consideration of the patient's general appearance, the presence of dyspnea and/or stridor, discoloration of the skin and mucous membranes due to cyanosis, assessment of the blood oxygen level (SpO<sub>2</sub>), and local clinical otorhinolaryngological findings. A clinical otorhinolaryngology examination with indirect laryngoscopy or fiber-optic nasopharyngolaryngoscopy was performed to establish the etiology of the obstruction or the possibility of intubation. Emergency surgical tracheostomy was performed under local anesthesia on an awake patient by a team of 2 physicians. A local anesthetic was applied to the whole incisional area, to the deep paratracheal planes (in the form of a combination of lidocaine and levobupivacaine). The leading surgeon was always an ORL-H&N surgeon, and the assistant was either an ORL-H&N surgeon, an emergency medicine physician, a trauma surgeon, a maxillofacial surgeon, or a resident, depending on the time and the circumstances of the tracheotomy. Patients were operated on in an operating room or other hospital facility when it was impossible to transport the patient to the operating room because of the urgency of airway management.

A standard surgical technique was used in these patients: a midline skin incision in Jackson's triangle, sharp dissection through the subcutaneous tissue, separation of the strap muscles from the midline, superior displacement of the thyroid isthmus with exposure of the anterior tracheal wall, an intercartilaginous horizontal tracheal incision between the second and fourth tracheal ring, and introduction of the cannula. The technique varied in cases of thyroidal tumors with tracheal displacement, laryngeal tumors with extralaryngeal spreading, and anterior neck metastases. Neck stiffness, a short and fat neck, and cervical spine deformity were considered difficult variants of neck anatomy. The existence of tumors, phlegmon, or metastases were considered as positive neck pathology. Tracheotomy complications and mortality during hospitalization were considered the main outcome measures.

Complications were noted and classified according to the time of their occurrence as follows: (1) intraoperative (which included bleeding, tracheostomy tube displacement, respiratory arrest, death), (2) early postoperative complications (which included subcutaneous emphysema, bleeding, pneumothorax,

tube displacement, tube obstruction, wound infection), and (3) late postoperative complications (which included granulomatous tissue formation, pneumonia, tracheoesophageal fistula, and tracheoinnominate fistula). Bleeding was considered a complication if further surgical reexploration for the control of bleeding was required (other than the use of a standard surgical technique). A lethal outcome that was the direct result of tracheotomy complications (operative or postoperative) was considered as tracheotomy related.

The factors that were analyzed and included in the logistic regression included demographic data (age and sex); body mass index (BMI, kg/m<sup>2</sup>); cause of airway obstruction; anatomical variations (neck stiffness, a short and thick neck, cervical spine deformity, an enlarged thyroid gland); pathological neck findings (primary tumors, deep neck space infections, metastases); the rate of intraoperative, early, and late postoperative complications; existing comorbidities; whether tracheotomy was performed in an operating room or not; previous radiotherapy or tracheostomy; and the mortality rate (tracheotomy related).

### Statistical Analysis

Descriptive statistics were calculated for demographic characteristics and other followed parameters and were presented as frequencies and proportions. Numeric data were tested for normal distribution using the Kolmogorov-Smirnov test and were nonparametric. The Mann-Whitney test was used to compare the numeric data (BMI and age). Categorical data were analyzed using Pearson chi-square test. For statistical analysis, univariable and multivariable logistic regression methods were used. All test variables with a statistical significance of  $P < .05$  in the univariable model were included in the multivariable model. Statistical significance was considered at  $P < .05$ . Statistical analysis was performed using the IBP SPSS Statistics v26 (Statistical Package for Social Sciences, SPSS Inc, Chicago, Illinois).

### Systematic Review

To compare the results of our study, we systematically examined the current literature on emergency surgical tracheotomy in terms of intraoperative and postoperative complication rates and mortality rates. PubMed, MEDLINE, the Cochrane Library, and World of Science databases were searched from their inception through June 2020. All English-language clinical trials, retrospective analyses, systematic reviews, and meta-analyses were included. Case reports were excluded, as well as studies with pediatric ( $<18$  years), nonhuman, or nonliving subjects. We also excluded studies of surgical tracheotomy performed in nonemergency settings and those describing surgical techniques without mention of intra- or postoperative complications. The terms “emergency tracheostomy” or “emergency tracheotomy” or “awake tracheostomy” or “awake tracheotomy” or “urgent tracheostomy” or “urgent tracheotomy” were used to identify relevant articles (with a word variation search). A list of titles was generated, and duplicate references were removed. Title and abstract reviews were

**Table 1.** Demographic and Clinical Characteristics of Patients Who Underwent Emergency Surgical Tracheotomy.

Characteristic	Complications, n (%)	No complications, n (%)	P value
<b>Sex</b>			
Male	96 (29.4)	231 (57.4)	.162
Female	16 (4)	59 (14.7)	
<b>Number of comorbidities</b>			
None	29 (7.6)	101 (25.1)	<.01
1	55 (14.4)	140 (34.8)	
2 or 3	14 (3.7)	29 (7.2)	
4 or more	7 (1.8)	7 (1.7)	
Missing	7 (1.8)	13 (3.2)	
<b>Smoking</b>			
Yes	107 (26.6)	272 (67.7)	.5
No	5 (1.2)	18 (4.5)	
<b>Anatomical variants</b>			
Yes	10 (2.5)	18 (4.5)	.357
No	82 (20.4)	216 (53.7)	
Missing	20 (5)	56 (13.9)	
<b>Neck pathology</b>			
Yes	29 (7.2)	37 (9.2)	<.01
No	82 (20.6)	250 (62.2)	
Missing	1 (0.2)	3 (0.8)	
<b>Tracheotomy done in the operating room</b>			
Yes	104 (25.9)	285 (70.9)	<.01
No	8 (2)	5 (1.2)	
<b>Previous radiotherapy</b>			
Yes	12 (3.1)	13 (3.2)	<.05
No	95 (24.5)	267 (66.4)	
Missing	6 (1.5)	9 (2.2)	
<b>Previous tracheotomy</b>			
Yes	8 (2)	4 (1)	<.01
No	104 (25.9)	286 (71.1)	

performed to identify articles for possible inclusion by 2 reviewers. Full articles were then obtained from this list and reviewed independently. Additional articles were included by reviewing the references of the included studies. The data extracted from each manuscript included the study setting, type of study, complication rate, complication type, and the mortality rate.

## Results

### Retrospective Review

The retrospective review of medical records included 402 patients who underwent emergency awake tracheotomy under local anesthesia in response to upper airway obstruction during a 5-year period. Male sex was more frequent (81.3% males vs 18.7% females). The average age of the patients was 60.4 years (SD  $\pm$ 11.3), with most patients in their sixth and seventh decades of life (68.1%; **Table 1**), and the average BMI was 23.3 (SD  $\pm$ 2.9); 195 (48.5%) of the

**Table 2.** Indications for Tracheotomy.

Indication for tracheotomy	n (%)
Malignant laryngeal neoplasm, primary	226 (56.2)
Malignant hypopharyngeal neoplasm, primary	35 (8.7)
Thyroid neoplasm	18 (4.5)
Undiagnosed neck mass	18 (4.5)
Recurrent malignant pharyngeal/laryngeal neoplasm	18 (4.5)
Malignant neoplasm of oral cavity and oropharynx, primary	17 (4.2)
Postirradiation edema	14 (3.5)
Bilateral laryngeal paralysis	14 (3.5)
Deep space neck infections	10 (2.5)
Postintubation stenosis	7 (1.7)
Trauma (face and neck)	7 (1.7)
Inflammation of the pharynx and larynx	6 (1.5)
Angioedema	5 (1.2)
Benign laryngeal neoplasm	4 (1.0)
Epistaxis	2 (0.5)
Tracheal neoplasm	1 (0.2)

patients had at least 1 comorbidity and 57 (14.2%) had 2 or more comorbidities. Cardiovascular disease was the most frequent comorbidity and was observed in 194 patients (48.3%), followed by psychological comorbidity in 40 patients (9.95%) and pulmonary diseases in 35 patients (8.7%). There was a significant relationship between the occurrence of complications and the number of comorbidities. Previously performed tracheotomy, the existence of pathological findings on the neck, previous radiotherapy, and the location where the tracheostomy was carried out (operating room or other hospital facilities) were significant factors for complication occurrence. There was a significant relationship between tracheotomy-related mortality and the location where the tracheostomy was performed (**Table 1**). There were no significant differences between older patients and those with a higher BMI with regard to tracheotomy-related mortality ( $P = .962$  and  $P = .392$ , respectively) and complication occurrence ( $P = .997$  and  $P = .205$ , respectively). The most common indications for tracheotomy were primary malignant tumors of the larynx and hypopharynx, followed by thyroid neoplasms, undiagnosed neck mass, and primary malignant tumors of the oral cavity and oropharynx (**Table 2**).

Complications were present in 111 (27.6%) of patients (**Table 3**). Bleeding was the most frequent intraoperative complication (5% of patients), followed by tracheostomy tube displacement and respiratory arrest. One patient died during the intervention. In the early postoperative course, subcutaneous emphysema and pneumothorax were the most frequent complications. Bleeding, wound infection, and tube obstruction were far less frequent. Considering late postoperative complications, cases of pneumonia (13 patients), tracheoesophageal fistula, and granulation tissue formation (both in 9 patients) were noted.

**Table 3.** Complications of Tracheotomy.

Complications of tracheotomy	n (%)
<b>Intraoperative</b>	
No	364 (90.55)
Yes	37 (9.2)
Bleeding	20 (5.0)
Tracheostomy tube displacement	10 (2.5)
Respiratory arrest	6 (1.5)
Death	1 (0.2)
Missing	1 (0.2)
<b>Early postoperative</b>	
No	340 (84.6)
Yes	62 (14.2)
Subcutaneous emphysema	18 (4.5)
Pneumothorax	14 (3.5)
Tracheostomy tube displacement	11 (2.7)
Bleeding	8 (2.0)
Wound infection	4 (1.0)
Tube obstruction	2 (0.5)
Missing	5 (1.2)
<b>Late postoperative</b>	
No	326 (81.1)
Yes	32 (7.6)
Pneumonia	13 (3.2)
Tracheoesophageal fistula	9 (2.2)
Granulation tissue formation	9 (2.2)
Tracheoinnominate fistula	1 (0.2)
Missing	45 (11.2)

According to univariable logistic analysis of complication occurrence, the number of comorbidities (odds ratio [OR] 1.4, 95% confidence interval [CI] 1.04-1.87), neck pathology (OR 2.4, 95% CI 1.38-4.13), tracheotomy performed outside the operating room (OR 4.38, 95% CI 1.4-14.28), previous radiotherapy (OR 2.59, 95% CI 1.14-5.88) and previous tracheotomy (OR 5.5, 95% CI 1.62-18.65) were all associated with a higher complication rate and further included in multivariable analysis. According to multivariable analysis, neck pathology (OR 2.05, 95% CI 1.1-4.77) and tracheotomy performed outside the operating room (OR 5.88, 95% CI 1.58-20) were significant positive predictors of the occurrence of

complications. Consistent with multivariable analysis, neck pathology stood out as a significant predicting factor (OR 3.07, 95% CI 0.7-13.48) of intraoperative complications. Significant predicting factors for early postoperative complications were neck pathology (OR 2.51, 95% CI 1.29-4.9) and tracheotomy performed outside the operating room (OR 5, 95% CI 1.51-20; **Table 4**). None of the predicting factors were significant for late postoperative complications occurrence according to multivariable analysis.

Diagnosis was not a significant predicting factor in univariable and multivariable analyses, but individual analysis of every diagnosis provided additional insights. Large thyroid neoplasms were a significant predicting factor of intraoperative complications in univariable analysis (OR 2.72, 95% CI 1.05-7.1,  $P < .05$ ) but not in multivariable analysis.

General in-hospital mortality was 4%, but a lethal outcome as a direct result of tracheotomy complications occurred in only 4 patients (1%). A fatal outcome ensued in 1 patient intraoperatively because of respiratory insufficiency. One patient died due to late postoperative complications resulting from tracheoinnominate fistula development. Two other patients developed pneumothorax as an early postoperative complication.

### Systematic Review

Overall, 659 studies were identified; 181 duplicates were removed, leaving 478 studies for title and abstract review. After title and abstract review, 445 were removed for failure to meet inclusion criteria. Full-text article review was performed for the remaining 33 articles. Twenty-six studies were further excluded either because they focused on surgical training techniques without mention of complications, they included pediatric patients (<18 years), or they reported the outcome of a mixed patient population (elective and emergency tracheotomy) without the possibility of distinguishing between complication rates that correlated only with emergency tracheotomies. The remaining 6 articles were included in the review. Six studies reported outcomes related only to emergency tracheotomy,<sup>6-9</sup> 1 reported outcomes related to emergency tracheotomy and emergency cricothyroidotomy,<sup>10</sup> and 1 reported outcomes related to emergency and elective tracheotomy<sup>11</sup> (**Table 5**). Complication occurrence varied from 2.7% to 57.3%. The most common complication was bleeding, whereas pneumonia, pneumothorax, tracheostomy tube obstruction, and subcutaneous emphysema were less

**Table 4.** Multivariable Logistic Regression of Tracheostomy Complications.

	Total complications		Intraoperative complications		Early postoperative complications	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Neck pathology	2.05 (1.1-4.77)	<.01	3.07 (0.7-13.48)	<.01	2.51 (1.29-4.9)	<.05
Tracheotomy performed outside the operating room	5.88 (1.58-20)	<.05			5 (1.51-20)	<.05

**Table 5.** Studies Evaluating Emergency Tracheotomy.

Authors	Year	Country	Type of study	Number of emergency tracheotomies	Age (mean)	Complications, n (%)	Complications details, n (%)	Tracheotomy-related mortality, n (%)
Gillespie and Eisele <sup>10</sup>	1999	United States	Retrospective review	14 (of 35 patients, 20 with cricothyroidotomy)	50	2 (14.2)	Bleeding 1 (7.1) Cricoid cartilage injury 1 (7.1)	0 (0)
Yuen et al <sup>9</sup>	2007	Singapore	Retrospective review	73	61.4	6 (8.2)	Bleeding 2 (2.7) Pneumothorax 1 (1.3) Wound infection 3 (4)	0 (0)
Altman et al <sup>8</sup>	2005	United States	Retrospective review	90	51.3	6 (6.7)	Pneumonia 2 (2.2) Respiratory arrest 2 (2.2) Tracheostomy tube displacement 1 (1.1) Bleeding 1 (1.1) Minor bleeding 2 (14.3) Major bleeding 1 (7.1) Subcutaneous emphysema 1 (7.1) Pneumothorax 1 (7.1)	0 (0)
Panajaroen and Tangtaturonrasme <sup>11</sup>	2015	Thailand	Prospective descriptive study	14 (of 100 tracheotomies, 86 with elective tracheotomy)	65	5 (35.7)	Immediate complications Bleeding 5 (7.4) Pneumonia 5 (7.4) Tracheostomy tube displacement 1 (1.5) Long-term complications Bleeding 5(7.4) Tracheostomy tube obstruction 4(5.9) Tracheostomy tube displacement 4 (5.9) Pneumonia 3 (4.4) Neck abscess 3 (4.4) Tracheitis 5 (7.4) Pneumothorax 2 (2.9) Granuloma 2 (2.9)	0 (0)
Fang et al <sup>7</sup>	2016	United States	Retrospective review	68	60.3	39 (57.3)	Bleeding 2 (5.4) Wound infection 2 (5.4) Pneumothorax 1 (2.7) Tracheostomy tube displacement 2 (5.4) Respiratory arrest 1 (2.7) Death 1 (2.7)	0 (0)
Sagiv et al <sup>6</sup>	2018	Israel	Retrospective review	37	64.6	9 (24.3)		1 (2.7)

common.<sup>6-12</sup> Reported tracheostomy-related mortality ranged from 0% to 2.7%.<sup>6-11</sup>

## Discussion

The attributes of the population who underwent emergency awake tracheostomy were similar throughout the literature. Most of the patients were male, in their sixth and seventh decades of life, with a primary or recurrent head and neck malignancy.<sup>6-8</sup> In this study, complications were present in 27.6% of individuals, with 1% tracheostomy-related mortality. These data are comparable with previously reported results presented in the systematic review.<sup>6-11</sup>

To date, the predicting factors for complication occurrence in emergency tracheostomy have not been the subject of published studies. It is important for patients and physicians to identify these factors to prepare, prevent, or manage unwanted outcomes during further treatment and care.

When facing emergency surgical tracheostomy, we need to emphasize the significant effect of pathological neck findings (including primary tumors, deep neck space infections, and metastases) on the occurrence of complications. The treatment of a number of patients with advanced locoregional oncological disease (laryngeal and hypopharyngeal squamocellular carcinoma) began with emergency surgical tracheostomy. The location and propagation of neoplastic infiltration can severely compromise the airway with possible tracheal infiltration or deviation, thus posing a higher risk for complications and mortality.<sup>12</sup> These circumstances can affect the exposure of critical anatomical landmarks, control of the operating field, and the duration of the procedure. Our data demonstrate that neck pathology significantly influenced the occurrence of intraoperative and early postoperative complications, pointing to the requirement for risk reduction with the involvement of experienced members of the surgery team in the procedure, mandatory collaboration with the anesthesiology team, and the acquisition of preoperative radiology imaging, if possible.

Tracheostomy performed outside the operating room (in other hospital facilities) was another significant predictor of all complications and of early postoperative complication occurrence. The lack of optimal conditions for surgical intervention, which include cauterization equipment, adequate lighting, and positioning of the patient, can lead to an uncontrolled situation and potential complications.

A few variables were not established as significant prognostic factors in multivariable analysis, but they had a statistically significant impact on complication occurrence in univariable analysis and deserve to be mentioned. Intraoperative tracheotomy complications were more likely to occur in patients with previously performed tracheostomy and radiotherapy. Irradiated and scarred tissue reacts poorly to new damage and is more prone to the development of wound complications.<sup>13,14</sup> Our findings suggest that these factors can increase intraoperative technical difficulties and prolong operative times, thus resulting in a higher rate of intraoperative complications, such as bleeding, tracheostomy tube displacement, and respiratory arrest. Previous studies

have reported that increasing comorbidity resulted in higher rates of postoperative infection, cardiac events, respiratory failure, and mortality in the late postoperative stage,<sup>15,16</sup> which was also established in our study. According to univariable analysis, the number of comorbidities was a significant risk factor for late postoperative complications and the occurrence of all complications, with pneumonia being the most frequent.

Tracheotomy-related deaths are rare events that happen mostly as a result of the surgical procedure or due to postoperative complications and during tracheostomy care. The results of a US survey reported by Das et al<sup>17</sup> identified 1000 serious incidents and events annually that were related to tracheotomies and 500 incidents resulting in death or permanent disability. Based on several review articles, the mortality rate for open surgical tracheotomy varied from 0.62% to 3%.<sup>18,19</sup> Risk factors reported in the literature included age, cardiac conditions, obesity, oncology patients on radiotherapy, and even the geographic location of the medical centers.<sup>17,20</sup> Our data support the fact that the intraoperative and early perioperative periods were a significantly sensitive time for the occurrence of a lethal outcome. The implementation of operative and postoperative protocols or checklists could ensure safe practice and help in reducing unwanted outcomes.

There are several limitations to our study. The study was retrospective, and the data extracted from the patients' medical records were limited in some cases. Also, indications for emergency tracheotomy were linked to the fact that most of the subjects were head and neck oncology patients. Patients in this group were in advanced stages of disease, with possible regional spreading of the disease, and they were candidates for radical surgery or organ preservation protocols. Large numbers of comorbidities, malnutrition, and a lower performance status were common occurrences. These factors may have contributed to the more frequent occurrence of certain tracheotomy complications, mortality rates, and emphasis on certain predicting factors that differed in other groups of patients (if they were more numerous). Lastly, despite a rather large number of patients in the cohort, the study was conducted in a single medical center. The predicting factors for complication occurrence and mortality after emergency surgical tracheotomy were not reported in any previous studies, and future multi-institutional investigations should provide more insight into this complex issue.

Emergency surgical tracheotomy is a necessary procedure for patients with acute airway obstruction or in cases of difficult nasotracheal or orotracheal intubation, and it is associated with a relatively low rate of complications and mortality. The specific characteristics of the patients present a risk for complications and a lethal outcome. The existence of neck pathology and situations in which tracheotomy was performed outside the operating room under uncontrolled conditions were significant prognostic factors for the occurrence of complications. Tracheotomy-related mortality was higher in patients with intraoperative and early postoperative complications.

Considering most patients who are candidates for emergency surgical tracheotomy, little can be done about certain prognostic factors to lower potential complications and to reduce mortality rates. Cases with extensive neck pathology must involve an experienced surgical team, an anesthesiology team, and radiology imaging, if the case urgency allows. Further directions should include the implementation of operative and postoperative protocols to ensure safe practice and to help in reducing unwanted lethal outcomes.

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### Author Contributions

**Ana D. Jotic**, substantial contributions to conception and design, analysis and interpretation of data, drafting the article, revising the article critically for important intellectual content, final approval of the version to be published, agreement to be accountable for all aspects; **Jovica P. Milovanovic**, substantial contributions to conception and design, analysis and interpretation of data, revising the article critically for important intellectual content, final approval of the version to be published, agreement to be accountable for all aspects of the work; **Aleksandar S. Trivic**, substantial contributions to conception and design, analysis and interpretation of data, revising the article critically for important intellectual content, final approval of the version to be published, agreement to be accountable for all aspects of the work; **Miljan M. Folic**, substantial contributions to conception and design, acquisition of data, drafting the article, final approval of the version to be published, agreement to be accountable for all aspects of the work; **Sanja B. Krejovic-Trivic**, substantial contributions to conception and design, acquisition of data, drafting the article, final approval of the version to be published, agreement to be accountable for all aspects of the work; **Zorana Z. Radin**, substantial contributions to conception and design, acquisition of data, analysis and interpretation of data, drafting the article, final approval of the version to be published, agreement to be accountable for all aspects of the work; **Marko N. Buta**, acquisition of data, drafting the article, final approval of the version to be published, agreement to be accountable for all aspects of the work; **Biljana R. Milicic**, analysis and interpretation of data, revising the article critically for important intellectual content, final approval of the version to be published, agreement to be accountable for all aspects of the work.

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