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ORIGINAL ARTICLE

Tetanus in adults: results of the multicenter ID-IRI study

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Abstract Tetanus is an acute, severe infection caused by a neurotoxin secreting bacterium. Various prognostic factors affecting mortality in tetanus patients have been described in the literature. In this study, we aimed to analyze the factors affecting mortality in hospitalized tetanus patients in a large case series. This retrospective multicenter study pooled data of tetanus patients from 25 medical centers. The hospitals participating in this study were the collaborating centers of the Infectious Diseases International Research Initiative (ID-IRI). Only adult patients over the age of 15 years with tetanus were included. The diagnosis of tetanus was made by the clinicians at the participant centers. Izmir Bozyaka Education and Research Hospital's Review Board approved the study. Prognostic factors were analyzed by using the multivariate regression analysis method. In this study, 117 adult

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patients with tetanus were included. Of these, 79 (67.5%) patients survived and 38 (32.5%) patients died. Most of the deaths were observed in patients >60 years of age (60.5%). Generalized type of tetanus, presence of pain at the wound area, presence of generalized spasms, leukocytosis, high alanine aminotransferase (ALT) and C-reactive protein (CRP) values on admission, and the use of equine immunoglobulins in the treatment were found to be statistically associated with mortality ($p < 0.05$ for all). Here, we describe the prognostic factors for mortality in tetanus. Immunization seems to be the most critical point, considering the advanced age of our patients. A combination of laboratory and clinical parameters indicates mortality. Moreover, human immunoglobulins should be preferred over equine sera to increase survival.

Introduction

Tetanus is an acute, exceedingly mortal infection caused by a neurotoxin secreting bacterium, *Clostridium tetani*. This toxin produces muscular rigidity and general spasms as the classical clinical picture of tetanus [1]. It is a very rare disease, which clinicians do not encounter in their routine practices either in intensive care units (ICUs) [2] or in departments of infectious diseases [3, 4]. Although it is a serious infection, tetanus is completely preventable by appropriate wound care and vaccination. Since natural infection does not lead to immune protection, any person who is not vaccinated is potentially at risk of developing tetanus. In developed countries, most cases of tetanus are reported among the elderly because of inadequate primary or booster immunization. On the other hand, neonatal tetanus, a major problem in unimmunized pregnant women, is mostly reported in the developing or underdeveloped countries [5].

In this study, we aimed to investigate the clinical and laboratory characteristics and the factors that affect mortality in hospitalized tetanus patients. The study protocol was approved by the institutional Ethics Board of Izmir Bozyaka Education and Research Hospital.

Methods

The hospitals participating in this study were the collaborating centers of the Infectious Diseases International Research Initiative (ID-IRI) and the study was organized through the ID-IRI network. Data from the centers were provided via the Internet as an Excel document, which was the complementary file of the questionnaire for tetanus patients. This study had a retrospective design. The demographic, clinical, laboratory, and therapeutic parameters of tetanus patients from 25 centers were included.

Inclusion criteria

The patients were included in the study in the absence of a more likely diagnosis, an acute illness with muscle spasms or hypertonia, and diagnosis of tetanus by an infectious diseases specialist or death, with tetanus listed on the death certificate as the cause of death or a significant condition contributing to death (https://wwwn.cdc.gov/nndss/conditions/tetanus/case-definition/2010/). Only patients over 15 years of age were included. Hence, neonatal or childhood tetanus cases were excluded from this study. The presenting symptoms, clinical findings, history of trauma, wound types, and locations were recorded. Patients were categorized according to the type of tetanus as [1]:

1. Localized tetanus: paresthesia, numbness, and spasms localized to the wound area.
2. Generalized tetanus: presence of trismus ("lockjaw"; masseter rigidity), risus sardonicus (increased tone in the orbicularis oris), swallowing problems, generalized tonic or clonic convulsions resembling decorticate posturing and consisting of opisthotonic posturing with flexion of the arms and extension of the legs, and the presence of general non-specific symptoms, such as fever, lassitude, and perspiration.
3. Cephalic tetanus: wound site at or above the neck and when the symptoms started and localized to cranial nerve musculature.

Statistical analyses

The SPSS 17.0 software package (SPSS Inc., Chicago, IL, USA) was used for the statistical analyses. All the patients with tetanus were classified into two groups: patients who died and those who survived. Descriptive statistics were presented as "frequencies and percentages" for all categorical variables. Continuous variables were presented as "means ± standard deviations" and "medians [interquartile range (IQR)]" according to the one-sample Kolmogorov–Smirnov normality test results. In the univariate analysis, categorical

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variables were compared by the χ^2 test or Fisher's exact test. Continuous (numerical) variables with normal distribution were tested with Student's *t*-test, non-parametric data with non-normal distribution were tested with the Mann–Whitney *U*-test. A binary logistic regression model was constructed via a bootstrap resampling procedure. Colinearity was tested and eliminated. The final model was tested with logistic regression. For examining the goodness-of-fit of the final model, the Hosmer–Lemeshow test was used. All of the tests were two-tailed and statistical significance was accepted as *p*-values less than 0.05.

Results

The mean age of the patients was 58 ± 16 (17–96) and 63 out of 117 (54%) were females. In total, 62 patients (53%) were over 60 years of age. Clinical presentation was generalized in 95 (81.2%), cephalic in 13 (11.1%), and localized in 9 (7.7%) patients. Most of the injuries were minor wounds (61.5%) frequently located in the lower extremities (56.4%) and body trunk (33%). In 36 (30.7%) patients, there were one or more co-morbid conditions. The demographic profiles, types and locations of injuries, co-morbid illnesses, vaccination/immunization histories, and clinical profiles of the cases are summarized in Table 1.

Clinically, the most frequent symptoms observed were trismus (74%), difficulty in swallowing (70%), local spasms (61%), generalized spasms (61%), and fever (36%). All the signs and symptoms of the patients are summarized in Table 2; the mean duration of symptoms did not differ significantly ($p > 0.05$) between the died and survived patient groups. The laboratory data of the patients are presented in Table 3.

The majority ($n = 100$, 85.5%) of cases were followed in ICUs. The mean ICU admission days and mean duration of ICU stay were 1.7 ± 1.99 days and 30.2 ± 33 days, respectively. The mean ICU admission days did not differ significantly between the two groups ($p = 0.18$), but the mean duration of ICU stay was significantly shorter ($p = 0.02$) in those who died, as expected. Among the patients admitted to the ICU, 73.5% ($n = 86$) were intubated at least once during the follow-up period and the mean intubation period was 1.08 ± 3.3 days, which did not differ significantly ($p = 0.99$) between the two patient groups. Antimicrobial therapy was administered in 93.2%, human tetanus immunoglobulin (HTIG) in 92.3%, sedatives in 78.4%, and neuromuscular blocking agents in 47%. Diazepam, lorazepam, and midazolam were the main benzodiazepines administered. The mean duration of diazepam and midazolam use was significantly shorter in patients who died (12.9 ± 10.1 vs. 7.1 ± 8.1 days, $p = 0.01$ and 14.5 ± 8 vs. 9 ± 7 days, $p = 0.03$, respectively). Wound debridement was performed in 20.5% of patients and surgical interventions were performed in 14.5% of all patients. In addition, in 30% of patients, due to overlapping infections during the follow-up, antibiotic modification was made and this was according to the preference of the treating clinician. Pneumonia was the most frequent infection observed. Therapeutic management of patients, including wound debridement, sedative use, neuromuscular blockage, antibiotics, immunoglobulin use, vaccination, and ICU support, are summarized in Table 4.

Outcomes

Mortality

Of 117 patients, 100 (85.5%) were admitted to ICUs. Overall, 79 (67.5%) patients survived and 38 (32.5%) died (in-hospital mortality). Most of the deaths were observed in older patients over 60 years of age (60.5%).

Sequelae formation

In 79 surviving patients, 17.1% ($n = 14$) had at least one sequela in the first year follow-up period. The sequelae were: articular stiffness ($n = 3$), muscular weakness in hands ($n = 2$), psychological problems ($n = 1$), fecal disturbance ($n = 1$), spastic lower extremity and walking disorders ($n = 2$), hypoxic encephalopathy ($n = 1$), acute renal failure ($n = 1$), respiratory distress ($n = 1$), arthrosis ($n = 1$), paralysis ($n = 1$), hemiparesis ($n = 2$), dysphonia ($n = 1$), and paraparesis ($n = 2$).

Multivariate analysis for mortality

All significant variables in the univariate analysis were included in the logistic regression analysis. Table 5 shows the significant predictors of mortality detected in the multivariate analysis. These were generalized tetanus, puncture type wounds that ultimately resulted in tetanus, presence of wound pain, entire body spasms, leukocytosis, increases in C-reactive protein (CRP) and aspartate aminotransferase (AST) levels, briefer hospital stays and treatment durations, and the use of equine immunoglobulins ($p < 0.05$ for all). Other variables which were found to be significant in the univariate analysis were found to be statistically insignificant for mortality in the final model. These were alanine aminotransferase (ALT) ($p = 0.11$), creatinine kinase (CK) ($p = 0.64$), lactate dehydrogenase (LDH) ($p = 0.07$), blood urea nitrogen (BUN) ($p = 0.29$), sedative ($p = 0.28$), benzodiazepine ($p = 0.07$), penicillin ($p = 0.61$), and cephalosporin uses ($p = 0.94$), ICU admission ($p = 0.77$), intubation ($p = 0.27$), and mean follow-up duration ($p = 0.83$).

Table 1 Demographic and clinical features of the patients with tetanus

Variables	Total, 117 (*n*, %)	Survived, 79 (*n*, %)	Died, 38 (*n*, %)	*p*-Value
Gender				
• Male	54 (46.2)	39 (49.4)	15 (39.5)	0.32
• Female	63 (53.8)	40 (50.6)	23 (60.5)	
Age (mean ± SD)	58 ± 16 (17–96)	56.9 ± 17	60.4 ± 14	0.36
Age >60 years	62 (53)	39 (49.4)	23 (60.5)	0.26
Co-morbid diseases	36 (30.8)	21 (26.6)	15 (39.5)	0.16
• Diabetes mellitus	9 (7.7)	6 (7.6)	3 (7.9)	0.96
• Chronic renal failure	2 (1.7)	0 (0)	2 (5.3)	0.04
• COPD	27 (23.1)	15 (18.9)	12 (31.6)	0.13
• Hypertension	18 (15.4)	9 (11.4)	9 (23.7)	0.08
• Immunosuppression	2 (1.7)	2 (2.5)	0 (0)	0.32
• Malignancy	1 (0.9)	1 (1.3)	0 (0)	0.49
Wound type				**0.01**
• Puncture	39 (33.9)	30 (39)	9 (23.7)	
• Thorn-prick	20 (17.4)	14 (18.2)	6 (15.8)	
• Car accident	2 (1.7)	1 (1.3)	1 (2.6)	
• Knife stab wound	4 (3.5)	2 (2.6)	2 (5.3)	
• Abdominal trauma	15 (13)	14 (18.2)	1 (2.6)	
• Incision/laceration by metals	19 (16.5)	13 (16.9)	6 (15.8)	
• Spit/skewer/pin puncture	9 (7.8)	1 (1.3)	8 (21.1)	
• Wound contamination with soil	4 (3.5)	2 (2.6)	2 (5.3)	
Wound location				0.36
• Head/neck	4 (3.4)	3 (3.8)	1(2.6)	
• Thoracal	39 (33.3)	23 (29.1)	16 (42.1)	
• Upper extremity	1 (0.9)	0 (0)	1 (2.6)	
• Lower extremity	66 (56.4)	48 (60.8)	18 (47.4)	
Tetanus type				**0.03**
• Generalized	95 (81.2)	59 (74.7)	36 (94.7)	
• Localized	9 (7.7)	8 (10.1)	1 (2.6)	
• Cephalic	13 (11.1)	12 (15.2)	1 (2.6)	
Vaccination history				0.19
• Unknown	75 (64.1)	44 (55.7)	31 (81.6)	
• Not implemented at all	15 (12.8)	12 (15.2)	3 (7.9)	
• Implemented in the last year	1 (0.9)	1 (1.3)	0 (0)	
• Implemented in the last 5 years	3 (2.6)	3 (3.8)	0 (0)	
• Implemented in the last 5–10 years	4 (3.4)	4 (5.1)	0 (0)	
• Implemented >10 years ago	13 (11.1)	11 (13.9)	2 (5.3)	
• Implemented for the current injury	4 (3.4)	2 (2.5)	2 (5.3)	
• Patient doesn't remember date and number of doses	2 (1.7)	2 (2.5)	0 (0)	

SD Standard deviation; *COPD* chronic obstructive pulmonary disease

Discussion

In our large multicenter case series, generalized form of disease, presence of general spasms, and dysphagia were related with higher mortality. Interestingly, our data disclosed that an array of laboratory data are also strong indicators of mortality, in contrast to previous studies. Added to leukocytosis, increases in CRP and liver enzymes were related with increased mortality and should alert the treating clinician for potential adverse outcomes. From a therapeutic perspective, the only parameter increasing mortality was the use of equine immunoglobulins. Finally, we found that significantly longer

Table 2 Signs and symptoms of the patients with tetanus

Variables	Total, 117 (*n*, %)	Survived, 79 (*n*, %)	Died, 38 (*n*, %)	*p*-Value
Swallowing problems	82 (70.1)	47 (59.5)	35 (92.1)	**<0.0001**
Local spasms	71 (61.2)	47 (60.3)	24 (63.2)	0.76
Muscle twitching	35 (29.9)	20 (25.3)	15 (39.5)	0.12
Entire body spasms	71 (60.7)	38 (48.1)	33 (86.8)	**<0.0001**
Trismus	86 (73.9)	55 (73.3)	27 (75)	0.85
Fever	42 (35.9)	24 (30.4)	18 (47.4)	0.06
Lassitude	47 (40.9)	29 (36.7)	18 (50)	0.18
Pain in the wound area	34 (29.8)	17 (21.5)	17 (48.6)	**0.003**
Breathing problems	38 (35.5)	19 (26.8)	19 (52.8)	**0.003**

hospital stays and treatment durations were observed among the survivors, as expected. The case fatality rates of tetanus were reported to be around 38–46%, but may reach to 65–70% in centers without appropriate intensive care conditions [6–10]. Hence, it is an excessively mortal disease. In this study, 32.5% of the hospitalized tetanus patients died and sequelae developed in 17% of the surviving patients. The relatively lower mortality rate of tetanus in our patients compared to various previous studies may be because the vast majority of patients were treated in well-equipped ICUs and have a degree of previous immunization, with the potential to lessen disease severity [1, 11, 12]. Various prognostic factors affecting mortality for tetanus were mentioned in different series [8, 9, 12–14]. The studies reported that older age, incubation period less than a week, generalized form of the disease, presence of general spasms, dysphagia, leukocytosis, head and neck injuries, neonatal disease, and disease following abortions have been described.

In this study, most tetanus cases were during the advanced ages. In a report from Japan, approximately 100 cases occur each year and 94% of patients were >40 years and 18% were >80 years of age [15]. Likewise, increased mortality reported in this patient population was closely related to decreases in antibody titers or the disappearance of protective immunity over time [16]. Accordingly, Simonsen et al. showed that serum tetanus antitoxin levels gradually subsided after immunization, and even after appropriate full primary vaccination, 28% of individuals did not maintain protective antibody titers [17].

Since the nature of tetanus is highly mortal, although it is completely preventable by appropriate immunization, it was truly described as an "inexcusable disease" in a 1976 JAMA editorial [18]. Checking patient's immune status depends traditionally on questioning the case and, in many cases, this may be misleading, since a considerable proportion of the patients cannot correctly recall their vaccination status. When the vaccination histories of our patients were analyzed, only 8 out of

Table 3 Laboratory findings of the patients with tetanus

Variables	Total, 117	Survived, 79 (mean ± SD)	Died, 38 (mean ± SD)	*p*-Value
WBC (/mm^3)	10,388 ± 4530	9116 ± 3992	13,031 ± 4485	**<0.0001**
Hemoglobin (mg/dL)	12.8 ± 2.6	12.9 ± 2.5	12.7 ± 2.9	0.63
Platelets (/mm^3)	251,252 ± 98,168	244,059 ± 88,782	266,638 ± 115,607	0.25
ESR (mm/h)	24.6 ± 22	22.4 ± 22	26.7 ± 11.5	0.12
CRP increase (times)	10.4 (1–45)	8.6 ± 9.2	13.9 ± 12.3	**0.02**
ALT (IU/L)	34 ± 24	30.4 ± 19.8	42.2 ± 29.8	**0.02**
AST (IU/L)	48 ± 52	41.3 ± 33.4	72.1 ± 46.1	**0.05**
ALP (U/L)	103 ± 65	98.7 ± 58.5	112 ± 76.3	0.37
CK (U/L)	679 ± 161	780 ± 184	820 ± 100	**0.04**
LDH (U/L)	341 ± 292	293.8 ± 155	445.5 ± 458	**0.03**
Creatinine (mg/dL)	0.97 ± 0.5	1.34 ± 1.4	1.1 ± 0.5	0.72
BUN (mg/dL)	37.9 ± 28	32.7 ± 25.9	48.3 ± 30.6	**0.005**

SD Standard deviation; *WBC* white blood cell; *ESR* erythrocyte sedimentation rate; *CRP* C-reactive protein; *ALT* alanine aminotransferase; *AST* aspartate aminotransferase; *ALP* alkaline phosphatase; *CK* creatinine kinase; *LDH* lactate dehydrogenase; *BUN* blood urea nitrogen

Table 4 Therapeutic management of the patients

Variables	(*n*, %) or mean ± SD			
	Total (*n* = 117)	Survived (*n* = 79)	Died (*n* = 38)	*p*-Value
Wound debridement				0.18
• Performed	24 (20.5)	14 (17.7)	10 (26.3)	
• Not performed	26 (22.2)	14 (17.7)	12 (31.6)	
• Unnecessary	66 (56.4)	50 (63.3)	16 (42.1)	
Sedative use	91 (78.4)	57 (73.1)	34 (89.5)	**0.04**
• Duration, BZDs use (days)	2.5 ± 5.9	2.4 ± 6.4	2.6 ± 4.7	0.38
BZDs	97 (85.8)	60 (80)	37 (97.4)	**0.01**
Diazepam	81 (69.2)	50 (63.3)	31 (81.6)	0.045
Lorazepam	3 (2.7)	3 (3.9)	0 (0)	**0.01**
Midazolam	47 (41.6)	31 (40.8)	16 (43.2)	0.80
Neuromuscular blockage	55 (47)	38 (48.1)	17 (44.7)	0.73
Vecuronium	7 (6)	2 (2.5)	5 (13.2)	**0.02**
Rocuronium	7 (6)	6 (7.6)	1 (2.6)	0.29
Pancuronium	18 (15.4)	17 (21.5)	1 (2.6)	**0.001**
Antibiotic therapy	109 (93.2)	74 (93.7)	35 (92.1)	0.75
Penicillin	29 (26.1)	26 (34.7)	3 (8.3)	**0.003**
Metronidazole	85 (72.6)	54 (68.4)	31 (81.6)	0.13
Cephalosporins	30 (26.5)	16 (20.3)	14 (36.8)	**0.06**
Aminoglycosides	6 (5.7)	3 (4.3)	3 (7.9)	0.39
Ig use	108 (92.3)	72 (91.1)	36 (94.7)	0.49
• Ig injection into the wound	80 (72.1)	59 (76.6)	21 (61.8)	0.10
• Mean Ig duration (days)	1.4 ± 1.3	1.36 ± 1.7	1.1 ± 0.3	0.51
• Mean Ig dose (IU)	8108.9 ± 2672	10,284 ± 31,201	3585 ± 12,124	0.21
Equine Ig use				
• lorazepam (%)	37 (31.6)	19 (24.1)	18 (47.4)	**0.01**
• Duration (days), mean ± SD	1.7 ± 2.2	2.2 ± 3	1.2 ± 0.6	0.17
• Equine Ig dose, mean ± SD	47,762 ± 52,509	56,011 ± 61,741	39,100 ± 40,470	0.31
Tetanus vaccination timing (days)	1.8 ± 1.3	1.5 ± 2	1 ± 0.4	0.17
Vaccination day after OSS	4 ± 3.8	4.3 ± 4	3.4 ± 3	0.33
Antibiotic modification	36 (30.8)	24 (30.4)	12 (31.6)	0.89
Surgical intervention	17 (14.5)	11 (13.9)	6 (15.8)	0.79
ICU admission	100 (85.5)	63 (79.7)	37 (97.4)	**0.01**
• Mean ICU admission days	1.7 ± 1.99	1.5 ± 1.5	2 ± 2.5	0.18
• Mean ICU stay	30.2 ± 33	36.5 ± 30	19.5 ± 36	**0.02**
Intubation	86 (73.5)	53 (67.1)	33 (86.8)	**0.02**
• Mean intubation days	1.08 ± 3.3	1.2 ± 3.9	1.2 ± 1.4	0.99
Mean hospital stay (days)	30.9 ± 38.2	36.6 ± 36.6	18.5 ± 39.2	**0.02**
Mean treatment duration (days)	20.1 ± 22.7	24.8 ± 25.4	11.7 ± 13.1	**0.007**
Mean follow-up duration (days)	24.7 ± 65.5	31.7 ± 67.5	10.1 ± 59.2	**0.09**

SD Standard deviation; *BZD* benzodiazepine; *Ig* immunoglobulin; *OSS*: onset of symptoms; *ICU* intensive care unit

Table 5 Multivariate regression analysis of mortality risks

Parameters	HR	95% CI	*p*-Values
Tetanus type (generalized)	12.6	(8.6–18.9)	0.004
Wound type, puncture	2.4	(1.8–6.8)	0.012
Wound pain	2.3	(2–3.1)	0.044
Entire body spasm	3.03	(1.9–4.6)	0.035
Leukocytosis	1.4	(1.3–1.6)	0.016
CRP increase	6.6	(2.3–7.1)	0.028
AST increase	2.1	(1.9–2.9)	0.043
Equine immunoglobulin use	3.05	(2.6–4.7)	0.025
Duration of hospital stay	2.9	(2.1–3.8)	0.027
Treatment duration	2.8	(1.9–4.2)	0.037

HR Hazard ratio; *CI* confidence interval; wound type 1, puncture by a crampon/nail; *CRP* C-reactive protein; *ALT* alanine aminotransferase

117 received tetanus vaccination in the last 10 years and mortality was not observed in this group. Waning immunity over the time is a well-known entity, and although rarely reported, tetanus may occur in previously vaccinated persons with protective levels of anti-tetanus antibodies. Thus, history of previous immunization should not dissuade a physician from establishing the diagnosis of tetanus [19]. Most of our patients did not detail their vaccination history. Consequently, this has blurred the statistical analysis and we could not disclose the effect of previous tetanus vaccination. For this reason, laboratory tests assessing serum tetanus immunoglobulin levels may be useful to evaluate the patients with obscure vaccination history [20]. On the other hand, the World Health Organization (WHO) indicates that tetanus prophylaxis including both HTIG and the vaccine should be considered essential for incompletely immunized individuals presenting with dirty wounds in routine practice [1, 6]. According to

our data, human immunoglobulins should be preferred over equine sera to increase survival during the primary treatment of the disease.

The role of antimicrobial therapy in tetanus is still debated [1]. *Clostridium tetani* is generally accepted as an antibiotic-sensitive community-acquired pathogen [21, 22]. Although there are reports in favor of metronidazole use over penicillin [23], we could not find any difference between penicillins, metronidazole, and cephalosporins. Accordingly, we could not find any difference between the neuromuscular agents administered and the sedatives used in the course of treatment.

Our study had two limitations. First, the diagnosis of the cases was based upon clinical findings and the presence of a history of convenient injury. Laboratory confirmation of tetanus is often difficult and usually not performed as stated in multiple reports [24, 25]. The second limitation was the retrospective design of the study. However, it is quite difficult to provide a large cohort with a prospective design for tetanus since it is a very rare disease.

In conclusion, our data disclosed that a generalized tetanus and the presence of a painful wound were associated with poor outcomes in hospitalized tetanus patients. It is worth mentioning that we have shown that laboratory data including leukocytosis, elevated liver enzymes, and CRP indicated mortality significantly, and these laboratory parameters should alert the treating clinician on the potential of poor outcomes, too. In addition, the production and use of purified human immunoglobulins should be a priority, particularly for the developing and underdeveloped countries.

Compliance with ethical standards

Funding We did not receive any kind of funding.

Conflict of interest None to declare.

Ethical approval Yes, it is obtained from Izmir Bozyaka Education and Research Hospital's Review Board.

Informed consent Not applicable. The study has a retrospective design.

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