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Clinical Outcomes of Patients Presenting with Pulmonary Embolism

Pulmoner Emboli ile Başvuran Hastaların Klinik Sonuçları

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Abstract

Objective: Acute pulmonary embolism is closely associated with severe morbidity and mortality. Treatment guidelines recommend taking rapid action and application of thrombolytic treatment in selected cases. The aim of this study is to evaluate the outcomes of thrombolytic treatment among our cases in accordance with the guidelines.

Materials and Methods: The clinical and demographic characteristics, concomitant diseases, predisposing factors, and treatment outcomes of 26 patients whom were diagnosed with pulmonary embolism and treated with 2 hours of infusion of 100 mg alteplase at diagnosis in our clinic between 2011 and 2015 were retrospectively evaluated.

Results: Data from 26 patients (M/F: 8/18) with a mean age of 65.8±17.1 years (30-86 years) and mean symptom duration of 58.9±72.4 hours (2-288 hours) were included in the analyses. Most frequent symptom and concomitant disease were shortness of breath (96.2%) and systemic hypertension (57.7%), respectively. Deep venous thrombosis was the predominant risk factor (69.2%). Pulmonary embolism was most frequently found in bilateral pulmonary arteries (42.3%). Mean pulmonary arterial systolic pressures before and after treatment were 54.5±5.9 (45-70) mmHg and 26.2±2.1 (22-30) mmHg, respectively. Two patients had minor hemorrhage after thrombolytic application, and all patient survived 1 year after treatment.

Conclusion: Most important factors for prognosis in pulmonary embolism are fast and accurate diagnosis, and appropriate treatment. Thrombolytic treatment can be administered safely and efficiently in selected cases with pulmonary embolism, and provides fast and significant clinical improvement in these patients.

Keywords: Pulmonary embolism, thrombolytic treatment, alteplase, trombolitik tedavi, alteplaz

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Öz

Amaç: Akut pulmoner emboli yüksek mortalite ve morbidite ile ilişkilidir. Tedavi klavuzları seçilmiş hastalarda trombolitik tedavi düşünülmesini ve tedavide hızlı davranılmasını önerir. Bu çalışmanın amacı pulmoner emboli hastalarında uyguladığımız trombolitik tedavilerin sonuçlarını kılavuzlar ışığında değerlendirmektir.

Gereç ve Yöntem: Kliniğimizde 2011 ile 2015 tarihleri arasında, pulmoner emboli tanısı konulan ve alteplaz 100mg dozunda 2 saat intravenöz infüzyon ile trombolitik tedavi uygulanan 26 hastanın klinik ve demografik bulguları, eşlik eden hastalıkları, predispozan faktörleri ve tedavi sonuçları değerlendirildi.

Bulgular: Analize dahil edilen 26 hastanın (E/K:8/18) ortalama yaşı of 65.8±17.1 yıl (30-86 yıl) ve ortalama semptom süresi 58.9±72.4 saat (2-288 saat) idi. En sık görülen semptom nefes darlığı (% 96,2) ve en sık eşlik eden hastalık sistemik arteriyal hipertansiyon (% 57,7) idi. Derin ven trombozu dominant risk faktörü idi (% 69.2). Pulmoner emboli en sık bilateral pulmoner arterlerde saptandı (% 42,3). Pulmoner arter sistolik basınçları tedavi öncesi ortalama 54.5±5.9 (45-70) mmHg ve tedavi sonrası ortalama 26.2±2.1 (22-30) mmHg idi. İki hastada trombolitik tedavi sonrası minör kanama saptandı ve tüm hastalar tedaviden 1 yıl sonra sağ kaldı.

Sonuç: Pulmoner embolide prognozu etkileyen en önemli faktörler doğru ve hızlı tanı konulması ve uygun tedavinin uygulanmasıdır. Pulmoner embolide seçilmiş olgularda trombolitik tedavi yüksek başarı oranı ile uygulanabilir ve hastaların klinik durumunda erken ve belirgin düzelme sağlar.

Anahtar Kelimeler: Pulmoner emboli trombolitik tedavi, alteplaz

Introduction

Today, pulmonary embolism (PE) is still an important cause of morbidity and mortality. It can be seen in a wide spectrum ranging from spontaneous detection in small vessels to advanced cardiological shock. The diagnosis of PE can be missed in many cases, but it can be completely treated once diagnosed. Current evidence suggests that about 5 to 10% of in-hospital mortality is associated with PE (1, 2). The mortality rate in untreated PE is about 30%, whereas 8% among treated cases (3).

The anticoagulant treatment is considered as the standard approach, because it prevents formation of new thrombus, as well as recovering already formed thrombus by triggering endogenous fibrinolytic activity. On the other hand, thrombolytic treatment (TT) actively lysis the thrombi. Rapid lysis of the thrombus enables early recovery of the pulmonary perfusion, maintaining the hemodynamic stabilization, gas exchange, and prevention of the right ventricle functions. Early initiation of the TT in PE can also decrease the long-term risk for developing permanent pulmonary hypertension by decreasing the thrombus burden. Mortality and morbidity are significantly decreased among PE cases who receive TT in acute phases (4).

Based on this background, this study aimed to evaluate the outcomes of TT in cases with PE to reveal the effectiveness of this treatment in this clinical condition that has a significant mortality and morbidity burden.

Materials and Methods

Patients and Study Design

A total of 108 patients were hospitalized with a diagnosis of PE between 2011 and 2015. The clinical probability of PTE using two different models (Wells and Wicki) twenty-six of the patients were classified as high risk or moderate-high risk, and included in this study. All cases were administered TT with alteplase (tPA). The study was conducted as a retrospective chart review.

High risk was characterized by a systolic arterial pressure <90 mmHg or a drop in systolic arterial pressure of at least 40 mm Hg for at least 15 minutes, or shock, or presence of a right atrial thrombus accompanying a PE. Moderate-high risk was defined as a class III-V PE severity index (PESI) or a simplified PESI (sPESI)>1, right cardiac failure in echocardiography and increased cardiac troponin-T levels.

Treatment Protocol

Routine biochemistry, complete blood count, activated partial thrombin time (aPTT), international normalization ratio (INR), arterial blood gas analyses, troponin T and plasma D-dimer levels were analyzed, and electrocardiography and bedside echocardiography were performed for all cases.Contrast-enhanced chest computerized tomography (CT) and/or lower extremity venous Doppler ultrasonography (USG) were performed based on the clinical profile of the patients.

The TT was administered at the coronary intensive care unit. A 100 mg of tPA was administered as 2 hours of infusion via peripheral intravenous access.Patients also received intravenous infusion of unfractioned heparin at 18 U/kg/hour after an 80 U/kg bolus dose on the first day. aPTT assessments every 6 hours during first 24 hours, and every 24 hours afterwards were performed and heparin dose was adjusted to maintain an aPTT level between 60 to 80 seconds. Warfarin was added to the treatment after the first day. Heparin treatment and combination regimen was continued for at least 5 days. When an INR level >2 was maintained for 2 consecutive days, heparin was stopped and recent warfarin dose was continued for at least 3 months in all patients without any underlying condition, for at least 1 year in patients with deep venous thrombosis or recurrent PE, and for much longer periods, e.g. lifetime, in patients with more severe underlying clinical conditions such as malignancy, etc..

The heart rates and systemic blood pressure levels, respiration rates, and oxygen saturations were monitored at 24^{th}-72^{nd} hours, 5^{th}-7^{th} days, and 1^{st}-3^{rd} months. Also, heart dimensions, left ventricle ejection fraction, and pulmonary arterial pressure levels were evaluated by transthoracic echocardiography at pretreatment period and posttreatment 24^{th}-72^{nd} hour, 5^{th}-7^{th} day, and 1^{st}-3^{rd} month assessments.

Statistical Analysis

Descriptive statistics were presented as mean and standard deviation for numerical variables, and frequency and percent for categorical variables. Comparisons between numerical variables between dependent groups were done using Friedman test. A p value lower than 0.05 was considered to be statistically significant. SPSS 21 (IBM Inc., NY, USA) was used for the analyses.

Results

A total of 26 patients (M/F: 8/18; 30.8% / 69.2%) were included in the study. Mean age of the patients were 62.1±21.1 years for males, and 67.2±15.7 years for females (p=0.819). Youngest and oldest male and female patients were aged 30 and 85, and 40 and 86, respectively. Nine patients were PESI Class-III (34.6%), 5 were Class-IV (19.2%), and 12 were Class-V (46.2%). Mean sPESI was 2.42. Thrombolytic treatment was initiated at the first 24 hours after PE in 9 patients (34.6%), between 24-74 hours in 12 patients (46.2%), and between 3-14 days in 5 patients (19.2%). General characteristics of PE cases are shown in the **(Table 1)**.

Table 1. General characteristics of the pulmonary embolism cases

	Mean±SD / n (%)
Age (year)	65.8±17.1
Gender	
Male	8 (30.8)
Female	18 (69.2)
Weight (kg)	83.0±10.9
Height (cm)	168.2±6.1
BMI (kg/m^2)	29.6±4.0
Risk group	
High risk	10 (38.5)
Moderate-high risk	16 (61.5)
PESI class	
Class III	9 (34.6)
Class IV	5 (19.2)
Class V	12 (46.2)
sPESI	2.4±0.6
Thrombolytic treatment	
24 hours	9 (34.6)
24-72 hours	12 (46.2)
3-14 days	5 (19.2)
Minor bleeding	2 (7.7)
Duration of hospitalization (day)	7.0±1.1

Eighteen patients (69.2%) had deep venous thrombosis as a predisposing factor for PE. Fifteen patients (57.7%) had systemic hypertension, 3 patients (11.5%) had surgical operation in more than 3 weeks prior to PE, 1 patient coronary by-pass operation, and two patients knee operation. Due to recurrent pulmonary embolism genetic testing was made one patient. This patient had gene mutation (3.8%), which was documented as hereditary thrombophilia, prothrombin C20210A mutation and protein C and S deficiency.

The presenting symptoms were dyspnea in 25 patients (96.2%), chest pain in 13 patients (50%), palpitation and syncope in 10 patients (38.5%). The electrocardiographic assessments revealed $S_1Q_3T_3$ pattern in 21 patients (80.8%), ST segment changes in 19 patients (73.1%), T wave inversion (V1-4) in 18 patients (69.2%), atrial fibrillation in 2 patients (%7.6), and sinus tachycardia in 16 patients (61.5%). Using bedside echocardiography right atrial thrombus were seen in 6 patients (23%). Right atrium thrombus were found to be mobile in 5 of these 6 patients and one patient had atrial fibrillation. Contrast enhanced chest CT imaging revealed that 8 patients (30.7%) had right, 7 patients (26.%) had left, 11 patients (42.3%) had bilateral pulmonary arterial embolism, and 6 patients (23.1%) had right atrial thrombus along with pulmonary artery embolism. Lower extremity venous Doppler USG assessments revealed that 9 patients had right DVT (34.6%), 6 patients had left DVT (23.0%), and 3 patients had bilateral DVT (11.5%). DVT were not detected in the patients with atrial fibrillation. Baseline clinical characteristics of the patients were summarized in **(Table 2)**.

Table 2. Baseline clinical characteristics of the patients

	n (%)
Comorbidities and risk factors	
Deep venous thrombosis	18 (69.2)
Systemic hypertension	15 (57.7)
Diabetes mellitus	4 (15.4)
Coronary artery disease	3 (11.5)
Immobilization	3 (11.5)
Surgery	3 (11.5)
Prior PE	3 (11.5)
Gene mutation	1 (3.8)
Provoked PE / Unprovoked PE	10 (38.5) / 16 (61.5)
Symptoms	
Dyspnea	25 (96.2)
Chest pain	13 (50)
Palpitation	10 (38.5)
Syncope	10 (38.5)
Cyanosis	9 (34.6)
Cough	8 (30.8)
Signs of DVT	7 (26.9)
Unilateral leg pain	2 (7.7)
Homans	1 (3.8)
Electrocardiographic findings	
S1Q3T3 pattern	21 (80.8)
ST segment changes	19 (73.1)
T wave inversion (V1-4)	18 (69.2)
Sinus tachycardia	16 (61.5)
Contrast-enhanced chest CT signs	
Right pulmonary artery embolism	8 (30.7)
Left pulmonary artery embolism	7 (26.9)
Bilateral main pulmonary artery embolism	11 (42.3)
Right atrial thrombus	6 (23.1)
Lower extremity venous Doppler USG	
Right deep venous thrombosis	9 (34.6)
Left deep venous thrombosis	6 (23.0)
Bilateral deep venous thrombosis	3 (11.5)
Normal findings	8 (30.7)

The vital signs of the patients at the pre-treatment and post-treatment follow-ups were presented in **(Table 3)**. Accordingly, the mean pre-treatment values of systemic arterial pressure were 100±17.3 / 67.2±10.4 mmHg, heart rate was 106.4±15.1 bpm, respiratory rate was 32.3±3.8 /minute, and oxygen saturation % was 85.8±2.7, which improved to 110±13.4 / 69.5±6.8 mmHg, 86.4±7.4 bpm, 22.4±1.4 /minute, and 93±1.3 % at the 24th-72nd hours post-treatment period, respectively. The improvements were statistically significant, and remained at the 5th-7th days, and stayed stable during the follow-ups.

Table 3. Vital signs at pre- and post-treatment assessments

	Pre-treatment	24th - 72nd hours	5th – 7th days	1st month	3rd month	p
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	
Systolic arterial pressure (mm Hg)	100±17.3	110.1±13.4	118.1±9	121.5±6.1	123.8±4.8	<0.001
Diastolic arterial pressure (mm Hg)	67.2±10.4	69.5±6.8	71.2±3.3	71.9±4	73.5±5.4	0.011
Heart rate (bpm)	106.4±15.1	86.4±7.4	76.7±6	70.9±5.3	71.5±4.8	<0.001
Respiratory rate (per minute)	32.3±3.8	22.4±1.4	19.5±1.6	17.1±1.9	16.8±0.8	<0.001
Oxygen saturation (%)	85.8±2.7	93±1.3	95±1.4	95.9±1.4	96±1.5	<0.001

The echocardiographic assessments during the treatment period and post-treatment follow-ups were summarized in **(Table 4)**. All patients had right heart failure and dilatation, right ventricle free wall hypokinesia, interventricular septum flattening, and paradox motion. Maximum and minimum pre-treatment pulmonary artery pressures were 70 mmHg and 45 mmHg, respectively. Pre-treatment left ventricle ejection fraction was over 50% in all patients. The mean end-diastolic right ventricle diameter, right atrium diameter, systolic pulmonary artery pressure, and left ventricle ejection fraction values were all improved significantly at the 24th-72nd hour assessments ($p<0.05$ for all). The improvements were remained during the post-treatment follow ups.

Table 4. Echocardiographic measurements

	Pre-treatment	24th - 72nd hours	1st month	3rd month
	Mean±SD	Mean±SD	Mean±SD	Mean±SD
Left ventricle ejection fraction (%)	52±2.1	56.9±2.9	59.7±1.8	62.5±4.6
Right ventricle end-diastolic diameter (apical four chamber)) (mm)	45.2±3.7	38.7±3	36.1±1.8	35.5±2.2
Right atrium diameter (apical four chamber) (mm)	46.5±3	40.2±2.9	36.5±3.8	36.5±3.3
Systolic pulmonary arterial pressure (mmHg)	54.5±5.9	33±3.6	28.1±2.2	26.2±2.1

Ten patients (38.5%) were at high-risk group, and 16 patients (61.5%) were at moderate-risk group according to their PE types. We performed thrombolysis to all our study participants. Alteplase treatment was applied successfully to all patients. The thrombus was completely lysed in 24th hour echocardiographic assessments in 6 patients with right atrial thrombus. One of those patients had syncope at supine position at the 60th minute of the treatment, which was thought to be associated with migration of lysed thrombus fragment into the pulmonary artery. Follow-up echocardiography revealed that the thrombus was completely lost in the right atrium, and the hemodynamics remained stable during hospital stay. Another patient, who had PE following a long duration trip, was admitted to the hospital in cardiopulmonary arrest condition, and TT was administered when the patient was intubated after a successful resuscitation. This patient has also completed the TT without any complications. Mean duration of hospitalization was 7.0±1.1 days in the study population. Minor bleeding, as a TT complication, was seen in 2 patients (7.7%). One of these patients had a cardiac catheterization by femoral access three days prior to TT, and had ecchymosis from inguinal to popliteal areas, which was associated with a 2 g/dL decrease in blood hemoglobin levels that resolved spontaneously without a need for transfusion. Other patient had ecchymosis at the left forearm vascular access area, which was also resolved spontaneously. None of the patients had one-year mortality.

Discussion

Complete or partial obstruction of pulmonary arterial flow in PE cases results with acute but reversible right ventricular insufficiency. The goal of treatment is rapid regaining of the obstructed pulmonary arterial flow, and prevention of early recurrence. Thrombolytic treatment should also be administered along with anticoagulant and supportive treatment in selected PE cases. Possible favorable effects of TT include hemodynamic stabilization, rapid improvement of symptoms, and prevention of PE complications. Today, there is still controversy about which PE cases should receive TT. Fibrinolytic treatment is recommended for high-risk PE cases, nevertheless it is not so clear for the patients with moderate PE risk (3, 5).

Acute high-risk PE cases have systemic hypotension or cardiogenic shock in addition to their general symptoms (6). The shock and hypotension are the most important indicators of the early mortality in acute PE (7). The TT is undoubtedly indicated as the first-step treatment in these patients unless contraindicated. It must be kept in mind that this group of patients should receive TT immediately, since the stable PE cases at admission can rapidly become decompensated, which can progress rapidly to hemodynamic deterioration and mortality.

The moderate-risk PE refers to cases without systemic hypotension but with right ventricle dysfunction and/or myocardial necrosis. Administration of TT to a selected subgroup of acute moderate-risk PE cases might be lifesaving. The mortality risk in these patients is increased, and they will gain benefit from the TT (8). This group of patients comprise about 40% of all PE cases, thus, achieving even a small mortality reduction should correspond to a significant benefit in mortality of all PE cases (3).

The non-randomized Management Strategy and Prognosis of Pulmonary Embolism Registry (MAP-PET) study was conducted in Germany with participation of 24 centers and 1001 patients, and showed that TT is effective to prevent recurrence in cases with PE and isolated right ventricle dysfunction, and also reported that mortality risk was increased if right ventricle functions were deteriorated during 15-month follow-up period (9). Subsequent analyses were also conducted to compare the efficiency of thrombolytics and heparin among 719 normotensive patients with right ventricular dysfunction (169 TT following heparin, 550 heparin only), which revealed that 30-days mortality and recurrence was significantly higher, but bleeding was significantly lower in patients who received heparin only. This study is the first that reported a survival benefit with TT in cases without shock (10).

Another study by Meneveau et al. evaluated the indicators for in-hospital clinical progress and long-term mortality in 249 cases with proven PE who received TT. Accordingly, initial right ventricle dysfunction was found to be resolved in 80% of the patients 48 hours after the TT. The presence of septal paradox movement after the treatment was identified as an independent predictor for poor in-hospital clinical progress. This study also revealed that early recovery of right ventricle functions might be an indicator for the efficiency of the TT (11).

The Pulmonary Embolism Thrombolysis (PEITHO) study has evaluated the effects of TT on long-term prognosis in patients with PE and right ventricle dysfunction or troponin positivity. During the seven days of follow-up, TT was found to have benefit for hemodynamic deterioration but not for reduction of mortality, also had increased risk of extracranial major bleeding and intracranial bleeding. About 70% of the patients (709 of 1006) were randomized in 28 centers, and followed-up for 2 years. Long-term survival was evaluated in 353 of 359 patients in TT arm, and 343 of 350 patients in placebo arm.

The mortality rates during a median 37.8 months of follow-up were 20.3% and 18% in TT and placebo arms, respectively. The dyspnea or functional disability among survivors was present in 36% of TT arm, and 30.1% of placebo arm. Echocardiographic assessments revealed that there was no difference regarding pulmonary hypertension and right ventricle functional failure between two arms. The chronic thromboembolic pulmonary hypertension rates were 2.1% and 3.2% in TT and placebo arms, respectively. According to these findings, one-third of moderate-risk PE patients have permanent functional disability, but chronic thromboembolic pulmonary hypertension is rare. The TT was found to have no benefit for long-term prognosis and functional disability (12). The PEITHO study revealed that long-term poor outcomes were mostly associated with the comorbid or underlying diseases, thus early initiation of TT is not able to prevent late outcomes, and this emphasizes the importance of close monitoring and rigorous follow-up of these patients regardless of the initial treatment approach selected.

The PE accompanies in 97% of the cases with right atrial thrombus, and the mortality rate was reported to be above 44% (13). The optimal treatment in PE patients with right heart thrombus is controversial. The European Cardiology Society and The American College of Chest Physicians guidelines considered these patients to have high-risk irrespective of hemodynamic stability, and immediate treatment is recommended for these patients (14, 15). The treatment options in PE cases with right atrial thrombus include TT, surgical removal, heparin only, or combination of these modalities. Another recent treatment option is catheter-directed thrombolytic treatment, namely EKOS, which uses ultrasound-facilitated catheter-directed thrombolysis. Nevertheless, this technique requires expertise, and can only be administered in certain centers. Apart from EKOS, regarding conventional methods for PE treatment, numerous studies reported that TT is more advantageous due to lower mortality risk (16). In a recent study by Nasrin et al., mortality rates associated with no therapy, anticoagulation therapy, surgical embolectomy, and thrombolysis were reported as 100%, 28.6%, 23.8% and 11.3 %, respectively in patients with right heart thrombo-emboli(17). Fragmentation of the thrombus after TT may result with embolization, but this generally not triggers severe hemodynamic consequences (18). In our study, six patients had right atrial thrombus that accompanies the PE. All these cases were treated successfully with TT. We suggest that TT should be the first-line treatment approach based on the clinical assessments in this patient group. Nevertheless, particularly for the intraatrial masses >60 mm, surgical removal or EKOS might be considered for the treatment keeping the pros and cons in mind (19).

Each PE patient should be evaluated individually for risks and benefits of TT. The thrombolytic medications in the treatment of PE include urokinase, streptokinase, alteplase, tenecteplase, and reteplase.

Primary mechanism of all thrombolytic agents is to convert the plasminogen to its active form of plasmin, which then destructs the fibrine and lyses the thrombus. Theoretically, the fibrin-specific agents like tenecteplase, reteplase, and alteplase affects the circulating procoagulant factors less and affects the fibrin-bound plasminogen more, and this is associated with reduced bleeding complication. Alteplase is the most commonly used fibrinolytic medication in PE, since it is specific to fibrin, and can be administered in a short time. The US Food and Drug Administration approved the 2-hour infusion of 100 mg dose of Alteplase in PE. Highest beneficial effects are observed in the first 48 hours of treatment, but this can be elongated up to 14 days (20, 21). The first 12-24 hours is critical for TT in acute myocardial infarct cases, but the first 2-weeks period is important for treatment benefit in PE cases. In our study, the symptom duration was between 2 to 288 hours in patients. The TT was administered successfully in patients with early and late admission.

The major complications of the TT is bleeding, allergic reactions, embolism, and stroke. Bleedings are most commonly seen in vascular access areas. Gastrointestinal, retroperitoneal and intracranial bleedings may also be seen. Intracranial hemorrhages are the most important cases among these. The intracranial hemorrhage risk with TT is about 1.2-3% (22, 23). In our study, none of the patients had major bleeding, but 2 patients had minor bleeding whom were completed the follow-ups without any problem. Nevertheless, the risk of bleeding, particularly the intracranial bleeding, should always be kept in mind when deciding to administer a TT treatment in these patients.

Limitations

The cases were retrospectively evaluated from the records of a cardiology department in a private practice health center. The patients with PE that treated in other departments of the center were not included due to unavailability of the records. This resulted with respectively low number of patients. The most important limitations of this study are the sample size and the retrospective design.

Conclusion

Each patient with PE should be evaluated individually and should be classified according to their risk group, for successful administration of TT if indicated. When all PE cases are considered, TT should be administered to the ones with high-risk, right atrial thrombus, moderate-high risk group, and deteriorated hemodynamics during follow-ups. Appropriate patient management with thrombolytic and/or anticoagulant treatment will significantly decrease the mortality and morbidity risk.

Ethics

Ethics Committee Approval: This study was approved by the Balikesir University Ethics Committee of the Faculty of Medicine (approval number:2019/104).

Informed Consent: Participants signed the written informed consent form.

Peer-review: Externally and internally peerreviewed.

Authorship Contributions: Concept: N.K.,T.Y.,E.A, Design: N.K.,T.Y,E.A, Supervision: N.K.,T.Y.,E.A., Fundings: N.K.,T.Y., Data Collection or Processing: N.K.,T.Y., Analysis or Interpretation: N.K.,T.Y.,E.A., Materials: N.K.,T.Y., Literature Search: N.K.,E.A, Writing: N.K., Critical review:N.K.,T.Y.,E.A.

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