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# Concomitant history of cancer in acute pulmonary embolism is connected with poorer outcome

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ABSTRACT

**Purpose:** Cancer increases the risk of venous thromboembolism (VTE) substantially. VTE is connected with poorer outcome in cancer patients. The aim of our study was to investigate the impact of cancer on the severity and short-term outcome of pulmonary embolism (PE). **Methods:** We retrospectively analyzed the data of 182 patients with confirmed PE. PE patients were subdivided in the group with concomitant active cancer disease or history of cancer or in the group without cancer. Groups were compared with Wilcoxon–Mann–Whitney Test. Logistic regression models were calculated to investigate the association between cancer and several parameters such as age and PE severity status as well as the association between in-hospital death and the parameters age, gender, PE severity status and cancer. **Results:** While 20.3% PE patients reported an active cancer disease or a history of cancer (64.9% female), 79.7% of the PE patients did not (60.7% female). PE patients with cancer were 5 years older (76.0 (65.5/81.0) vs. 71.0 (58.5/80.5) years, $P = 0.055$) and revealed a higher PE severity status in mean ($1.91 \pm 0.53$ vs. $1.67 \pm 0.54$, $P = 0.069$). Univariate logistic regression models showed an association between cancer and age (OR 1.04, CI 95% (1.01–1.08), $P = 0.017$) as well as cancer and the severity status (OR 2.38 (1.05–5.26), $P = 0.037$). In-hospital death in the early course was strongly

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*Abbreviations:* AHA, American Heart Association; cTnI, cardiac Troponin I; CT, computed tomography; CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; ECG, electrocardiography; ESC, European Society of Cardiology; PE, pulmonary embolism; RBBB, right bundle-branch block; RV, right ventricle; RVD, right ventricular dysfunction; RVF, right ventricular failure; SAE, serious adverse event; SD, standard deviation; sPAP, systolic pulmonary artery pressure; V/Q scan, ventilation–perfusion scan.

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connected with the PE severity status (OR 36.60 (2.99–448.68), $P = 0.0049$), but not with cancer ($P = 0.65$). **Conclusions:** Concomitant history of cancer in acute PE was associated with higher PE severity status and therefore poorer outcome.



## Introduction

Cancer increases the risk of venous thromboembolism (VTE = pulmonary embolism (PE) + deep vein thrombosis (DVT)) substantially [1, 2]. Patients with cancer reveal a 4- to 7-fold higher risk to develop a venous thromboembolic event in comparison to those patients without cancer [2–6]. The association between cancer and VTE is well known for a long time. As long ago as in the 19th century Armand Trousseau first described an association between cancer and venous thrombotic events [2, 6, 7].

Besides the higher risk to develop a VTE, VTE in patients with cancer is connected with poorer outcome and shorter survival [2, 3, 8–15]. VTE is – besides the cancer itself – the second leading cause of death in patients with cancer [2]. However, most of the studies do not differentiate between PE and DVT, but investigate VTE in general.

The aim of our study was to investigate the impact of cancer on the severity status of PE and on in-hospital death of the PE patients.

## Methods

### *Study design*

We performed a retrospective analysis of all patients with a confirmed diagnosis of acute PE, who were treated at the internal medicine department between May 2006 and June 2011. Medical records of 182 consecutive PE patients were reviewed for medical history (symptoms and history), examinations (transthoracic 2D-echocardiography, CT, V/Q-scan, Doppler ultrasound of the leg veins) and laboratory parameters.

In studies with retrospective analysis of diagnostic standard data no ethic statement is needed in Germany.

### *Enrolled subjects*

Patients were eligible for our study if they were at least 18 years old, treated in the internal medicine department of the hospital and had a confirmed acute PE. The patients were identified by performing a search on the hospital information system database for the diagnostic code of PE (ICD-10-Code I26).

Confirmation of PE was defined if the patient had one of the following criteria:

1. Computed tomography (CT) pulmonary angiogram of the chest with an identified filling defect in the pulmonary artery system.
2. Positive venous ultrasound of an extremity consistent with DVT in patients with typical symptoms of PE (chest pain or dyspnea) and positive D-dimer.
3. Scintigraphic ventilation–perfusion (V/Q) scan read as high probability for PE.

All of the radiographic images were analyzed by experienced radiologists. If the diagnosis of PE was not confirmed by these criteria, then the patients were not included in this study.

### *Study groups*

In this study, PE patients were subdivided into 2 groups:

1. **PE + cancer** group with PE patients with concomitant active cancer disease or a history of cancer. We did not differentiate types of cancer.
2. **PE − cancer** group without concomitant cancer or history of cancer.

### *Laboratory examinations*

We focused for laboratory examinations on the levels of cardiac Troponin I (cTnI), CK, creatinine and D-dimer. A myocardial necrosis was defined as an elevation of cTnI value >0.1 ng/ml. D-dimer measurements were performed using an enzyme linked immunosorbent assay. D-dimer elevation was defined as a D-dimer value of >0.110 mg/l.

### *Severity status of PE*

The PE severity status was defined according to the European Society of Cardiology (ESC) guidelines and AHA scientific statement [16, 17]. PE patients with a systolic blood pressure of <90 mmHg were classified as high-risk PE patients (massive PE = PE status 3 in statistical calculation) [16, 17]. Normotensive PE patients were included in the non-high-risk PE patient group [17]. Further classification of hemodynamic stable patients was made according to the RVD and the biomarker levels (especially cTnI) [17].

RVD was defined according to the AHA scientific statement [16] as a right ventricular (RV) septal–lateral diameter in 4 chamber view in a CT or echocardiography divided by a left ventricular (LV) septal–lateral diameter >0.9 [16]. Moreover, the RVD was defined as RV hypokinesis and tricuspid regurgitation in echocardiography [16]. Pulmonary artery pressure was measured as systolic pulmonary artery pressure (sPAP) in a 4-chamber view of transthoracic echocardiography.

Normotensive PE patients (non-high-risk PE patients) were classified as patients with intermediate risk due to existing RVD or positive biomarker levels as cTnI (submassive PE = PE status 2 in statistical calculation), and PE patients with low

risk without RVD and with negative biomarker levels (low-risk PE = PE status 1 in statistical calculation) [16, 17].

### *Study parameters*

The retrospectively analyzed parameters included patients' baseline characteristics and history, risk factors, clinical characteristics of the PE event, laboratory findings, ECG data, echocardiography, radiographic findings and death in the hospital. The ECG was evaluated for complete or incomplete right bundle branch block (RBBB) and $S_I$-$Q_{III}$-type.

### *Statistics*

Clinical characteristics, laboratory findings, radiographic and echocardiographic data and in-hospital death were compared. The commercially available software BIAS® (version 10.04) was used for the computerized analysis. Statistical analysis of the 2 groups was performed using the Wilcoxon–Mann–Whitney Test. For statistical comparison of the PE severity status of the two groups the PE severity status was analyzed as PE status 1 to 3, like mentioned above.

Moreover univariate logistic regression models were calculated for the association between cancer and the parameters age, gender, PE severity status, lung infarction with pneumonia, DVT, chest pain, dyspnea, haemoptysis syncope, surgery or trauma in the last 3 months before PE event, VTE event in patient's history and RVD as well as cancer and the parameters cTnI, CK, creatinine, D-dimer, systolic and diastolic blood pressure, RBBB, $S_I$-$Q_{III}$-type and sPAP. Furthermore a logistic regression model for the association between in-hospital death and the parameters age, gender, PE severity status and cancer was performed.

*P*-values of $<0.05$ were considered as statistically significant.

## Results

Between May 2006 and June 2011, a total number of 182 patients (61.5% female) with confirmed PE were included in this study. Mean age of the PE patients was $68.5 \pm 15.3$ years (female: $70.8 \pm 15.1$ years; male: $64.9 \pm 15.0$ years). PE diagnosis was confirmed in 156 patients (85.7%) using CT. In 19 patients V/Q scan (10.4%) leads to the diagnosis and in 7 patients (3.8%) diagnosis was made by positive venous ultrasound of an extremity, which was consistent with DVT in patients with typical symptoms of PE (chest pain or dyspnea) and positive D-dimer value.

Out of the 182 PE patients, 7 patients (3.8%) presented with hemodynamic instable PE (high-risk PE patients) and 175 PE patients (96.2%) were normotensive and classified as non-high risk PE patients. Eighty-eight normotensive PE patients (50.3%) showed RVD in the echocardiography and/or CT and/or positive cTnI levels (PE with intermediate risk = submassive PE) and 87 patients (49.7%) were classified as non-high-risk PE without RVD or cTnI elevation (low risk PE). Five patients (2.7%) died an in-hospital death.

Thirty-seven (20.3%) PE patients had an active cancer disease or a history of cancer (64.9% female). In contrast 145 (79.7%) of the PE patients did not show a concomitant known cancer disease or history of cancer (60.7% female).

PE patients with concomitant active cancer disease or history of cancer were in median 5 years older (76.0 (65.5/81.0) vs. 71.0 (58.5/80.5) years, $P = 0.055$) (Fig. 1) and revealed a higher PE severity status in mean ($1.91 \pm 0.53$ vs. $1.67 \pm 0.54$, $P = 0.069$) with a trend toward significance. Patients' characteristics were shown in Table I. The frequency of PE patients with known cancer diseases increases over the age groups (Fig. 2).

While more than 1/3 of the PE patients without cancer had a low-risk PE, only less than 1/5 of the PE patients with concomitant active cancer disease or history of cancer were classified as low-risk PE. The majority of PE patients of both groups were in the submassive PE status (PE + cancer 71.9% vs. PE – cancer 59.5%). The percentage of high-risk-PE was higher in PE + cancer group than in PE – cancer (9.4% vs. 3.6%) (Tab. I).

Univariate logistic regression models showed an association between cancer and age (OR 1.04, CI 95% (1.01–1.08), $P = 0.017$) as well as cancer and PE severity status (OR 2.38, CI 95% (1.05–5.26), $P = 0.037$) and the symptom of chest pain (OR 0.34, CI 95% (0.12–0.98), $P = 0.045$) (Tab. II), but not with the examined laboratory markers (Tab. III). An in-hospital death in the early course was strongly connected with the PE severity status (OR 36.60 (2.99–448.68), $P = 0.0049$), but not with known cancer ($P = 0.65$) (Tab. IV).

## Discussion

Cancer and its treatments are well-known risk factors for both VTE-entities, for PE as well as DVT [3, 6, 8, 10, 11, 18–21]. In addition, VTE is a well-recognized complication of malignant diseases [5, 6, 22–24]. The potential life-threatening VTE entity of PE is significantly more common among cancer patients than in those without [25, 26]. Moreover patients with acute VTE have an increased risk of occult malignancy [6, 7, 27–31]. The VTE risk in each cancer patient varies, depending on cancer-specific and patient-specific factors [3, 5, 6, 10]. Cancer-specific factors are tumor type and

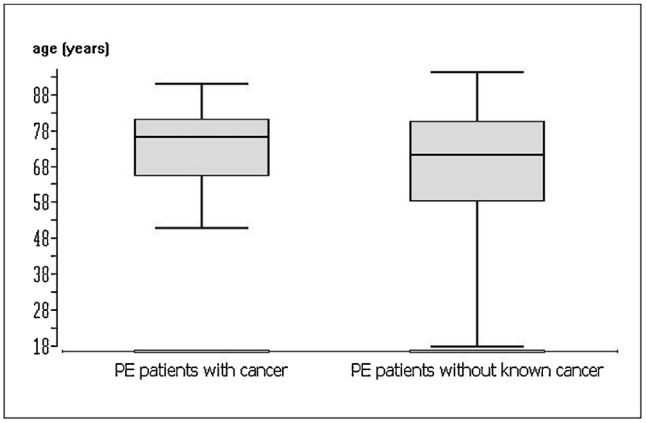


**Fig. 1 – Age of the PE group with and without known cancer. Box plots with median and per quartiles**

**Table I – PE patients' characteristics. P-values of <0.05 were considered as statistically significant**

| | PE + cancer PE patients with concomitant active cancer disease or cancer in history | PE – cancer PE patients without concomitant known cancer or history of cancer | P-value |
|---|---|---|---|
| *Age (Median, quartile)* | 76.0 (65.5/81.0) years | 71.0 (58.5/80.5) years | 0.055 |
| *Gender (females)* | 64.9% | 60.7% | 0.64 |
| *PE status (mean ± SD)* | 1.91 ± 0.53 (Low risk PE: 18.8%, submassive PE: 71.9%, massive PE: 9.4%) | 1.67 ± 0.54 (Low risk PE: 36.9%, submassive PE: 59.5%, massive PE: 3.6%) | 0.069 |
| *In hospital death* | 2.7% | 2.8% | 0.99 |
| *Lung infarction with pneumonia* | 40.1% | 46.2% | 0.54 |
| *DVT* | 73.0% | 64.8% | 0.35 |
| *Surgery or trauma in the last 3 months before PE event* | 13.5% | 19.3% | 0.42 |
| *VTE event in patients' medical history* | 18.9% | 25.2% | 0.43 |
| *Symptoms at admission* | | | |
| Chest pain | 21.6% | 35.9% | 0.10 |
| Dyspnea | 24.3% | 17.2% | 0.33 |
| Haemoptysis | 2.7% | 3.5% | 0.82 |
| Syncope/collapse | 8.1% | 11.7% | 0.53 |
| Systolic blood pressure (mean ± SD) | 139.51 ± 33.30 mmHg | 144.68 ± 29.40 mmHg | 0.55 |
| Diastolic blood pressure (mean ± SD) | 75.76 ± 19.81 mmHg | 77.86 ± 19.76 mmHg | 0.58 |
| *ECG parameters* | | | |
| Heart rate per minute (mean ± SD) | 95.35 ± 17.61 beats/min | 93.41 ± 26.51 beats/min | 0.22 |
| RBBB | 8.8% | 14.2% | 0.63 |
| $S_I$-$Q_{III}$-type | 8.8% | 9.9% | 0.92 |
| *Transthoracic echocardiography* | | | |
| RVD | 70.0% | 56.1% | 0.27 |
| sPAP (mean ± SD) | 36.91 ± 21.18 mmHg | 33.38 ± 17.61 mmHg | 0.54 |
| sPAP > 30 mmHg | 68.2% | 58.0% | 0.46 |
| sPAP > 50 mmHg | 13.6% | 13.4% | 0.99 |
| *Laboratory parameters* | | | |
| cTnI (mean ± SD) | 0.15 ± 0.22 ng/ml | 0.12 ± 0.29 ng/ml | 0.16 |
| CK (mean ± SD) | 70.97 ± 66.59 U/l | 98.37 ± 188.15 U/l | 0.070 |
| Creatinine (mean ± SD) | 1.07 ± 0.29 mg/dl | 1.11 ± 0.38 mg/dl | 0.98 |
| D-dimer (mean ± SD) | 3.12 ± 4.12 mg/l | 2.56 ± 3.46 mg/l | 0.35 |

stage, cancer-therapy as surgery or chemotherapy and/or supportive regimes [1, 3, 6, 10, 32, 33]. Patient-specific factors comprise history of previous VTE, obesity, co-morbidities, higher age, genetic predisposition and high leukocyte and platelet counts [1, 3, 10, 34]. Besides the higher risk to develop a VTE event in cancer patients, VTE in patients with cancer is strongly connected with elevated complication rate, like recurrent VTE or bleeding events [11, 35–37], poorer outcome and shorter survival [2, 3, 8–10, 22, 31, 34, 38–40]. Besides the cancer itself, VTE is the second leading cause of death in patients with cancer [2, 5, 30]. Especially PE is an important cause of death in cancer patients [11]. However, most of the studies do not differentiate between the entities of PE and DVT, but investigate VTE in general.

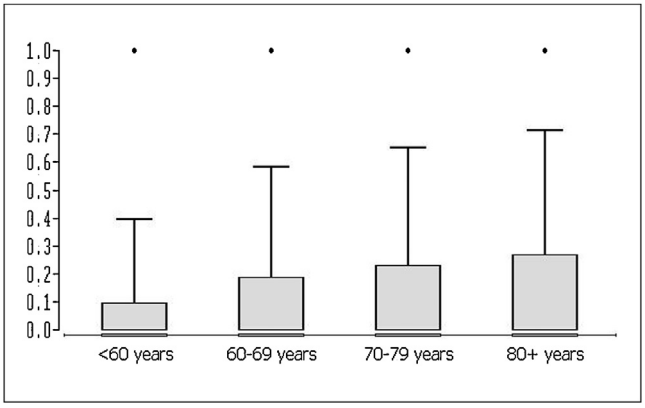


**Fig. 2 – Percentage of PE patients with active cancer disease or cancer in history in the age groups <60 years, 60–69 years, 70–79 years and 80+ years**

The aim of our study was to investigate the impact of cancer on the PE severity status and short-term outcome of the PE patients.

The results of our study showed a strong association of cancer with higher PE severity status. PE patients with active cancer disease or history of cancer revealed a 2.4-fold higher risk for advanced PE severity status than those PE patients without cancer. Accordingly, PE patients with cancer had higher percentages of submassive as well as massive PE status than those without cancer.

Our study failed to confirm a significant direct association between cancer and in-hospital death, although PE severity status was strongly associated with in-hospital

**Table II – Univariable logistic regression model to analyze the association between cancer and the parameters age, gender, PE status, lung infarction with pneumonia, DVT, chest pain, dyspnea, haemoptysis, syncope/collapse, surgery or trauma in the last 3 months before PE event, VTE event in patients' medical history and RVD. P-values of <0.05 were considered as statistically significant**

| | OR (95% CI) | P-value |
|---|---|---|
| *Active cancer disease or cancer in patients' medical history* | | |
| Age | 1.04 (1.01–1.08) | **0.017** |
| Gender | 1.02 (0.44–2.33) | 0.97 |
| PE severity status | 2.38 (1.05–5.26) | **0.037** |
| Lung infarction with pneumonia | 0.74 (0.32–1.69) | 0.47 |
| DVT | 1.96 (0.73–5.26) | 0.18 |
| Chest pain | 0.34 (0.12–0.98) | **0.045** |
| Dyspnea | 0.58 (0.20–1.69) | 0.33 |
| Haemoptysis | 0.91 (0.10–8.33) | 0.93 |
| Syncope/collapse | 0.90 (0.23–3.45) | 0.87 |
| Surgery or trauma in the last 3 months before PE event | 0.79 (0.26–2.33) | 0.67 |
| VTE event in patients' medical history | 0.69 (0.25–1.89) | 0.47 |
| RVD | 1.59 (0.66–3.84) | 0.31 |

death, as we had expected and cancer was additionally associated with PE severity status. Higher PE severity status revealed a 36.6-fold increased risk of in-hospital death. Therefore, a higher PE severity status in PE patients with cancer is not a minor result, but rather an important outcome result. A higher age in PE patients with cancer is not surprising. An association between many cancer entities and aging process is well known [6, 41].

Several studies have shown a poorer outcome of VTE patients with malignancy in comparison to those without and therefore are in coherence with the results of our study [5, 8, 9, 13, 42]. Already in 1980, Shen and Pollak [43] reported a 1.8-fold higher frequency of fatal PE in cancer patients than in those patients without cancer [43]. Also Carson et al. [12] described a 3.8-fold increased 1-year mortality in PE patients

**Table III – Univariate logistic regression model to analyze the association between cancer and the parameters cTnI, CK, creatinine, D-dimer, systolic blood pressure, diastolic blood pressure, heart rate, RBBB, $S_I$-$Q_{III}$-type and sPAP. P-values of <0.05 were considered as statistically significant**

| | OR (95% CI) | P-value |
|---|---|---|
| *Active cancer disease or cancer in patients' medical history* | | |
| cTnI | 1.08 (0.17–6.67) | 0.93 |
| CK | 1.01 (1.00–1.03) | 0.11 |
| Creatinine | 1.41 (0.38–5.26) | 0.61 |
| D-dimer | 0.94 (0.85–1.04) | 0.23 |
| Systolic blood pressure | 1.01 (0.99–1.03) | 0.45 |
| Diastolic blood pressure | 1.00 (0.97–1.02) | 0.91 |
| Heart rate | 0.99 (0.97–1.01) | 0.59 |
| RBBB | 1.45 (0.29–7.14) | 0.65 |
| $S_I$-$Q_{III}$-type | 1.16 (0.23–5.88) | 0.85 |
| sPAP | 0.99 (0.97–1.02) | 0.64 |

**Table IV – Univariate logistic regression model to analyze the association between in-hospital death and the age, gender, PE status and cancer. P-values of <0.05 were considered as statistically significant**

| | OR (95% CI) | P-value |
|---|---|---|
| *In-hospital death* | | |
| Age | 1.11 (0.95–1.29) | 0.17 |
| Gender | 0.72 (0.06–8.33) | 0.79 |
| PE stadium | 36.60 (2.99–448.68) | **0.0049** |
| Active cancer disease or cancer in patients' medical history | 1.75 (0.15–0.05–20) | 0.65 |

with presence of cancer in comparison to those without cancer [12]. In coherence, Levitan et al. [8] found a 3.2-fold higher risk of death after VTE event and a 3-fold higher risk of recurrent VTE in cancer patients than in those without in the first 183 days after VTE event [8]. Also Goldhaber et al. [9] identified cancer as a significant prognostic factor in PE in the ICOPER study [9]. PE patients with concomitant cancer disease revealed a 2.3-fold higher mortality after PE event in the first 3 months compared to PE patients without cancer [9]. Monreal et al. [11] reported a 1.8-fold higher risk of fatal PE and a 3.3-fold higher frequency of fatal bleedings in PE patients with cancer than in those PE patients without cancer in the first 3 months after symptomatic PE event [11]. The study results of Prandoni et al. [35] revealed higher percentages of recurrent VTE and bleedings in DVT patients [35]. Moreover cancer diagnosed in the first year after VTE event was connected with advanced stage of cancer and poorer prognosis in the study of Sorensen et al. [44] Therefore, several study results are in coherence with our study and confirm this link between cancer and VTE [31].

The pathogenesis of VTE and blood coagulation activation in cancer patients is multi-factorial and complex [3, 5, 18, 23, 24, 31, 34]. Especially cancer growth process is associated with hypercoaguable state [23, 24, 45]. Also cancer patients without thrombosis commonly present with hypercoagulation seen in the laboratory coagulation tests [23, 24]. Tumor cells activate the coagulation and haemostatic system on the one hand; on the other hand the tumor can compress the venous system, which results in stasis of blood flow and cancer patients often have to undergo surgery more frequently, chemotherapy with or without adjuvant supportive and/or hormone therapy and radiotherapy with concomitant hospitalization, reduced mobility and central venous catheters [5, 24, 31, 46–48]. The activation of the haemostatic system by tumor cells involves several haemostatic pathways [1, 3, 5, 23, 24, 31, 45]. A major role play tumor cell-specific clot promoting properties [3, 31]. Key factors are tumor factor expression, elevation of haemostatic markers, inflammatory cytokines, acute phase reactants, tissue factor as well as cancer proagulant and paraprotein production, adhesions of tumor cells with platelets, endothelial cells as well as leucocytes, necrosis (factors) and elevated production of microparticels and cytokines by tumor cells or host cells [1, 3, 24, 31, 45, 48]. Activation of the coagulation cascade and haemostatic cellular components are leading to thrombin

generation and fibrin formation [3, 24, 31]. Moreover proteins and cellular components of haemostasis and coagulation seem to play an important role in tumor neoangionesis and metastasis formation at the same time [3, 23, 24, 30, 31, 45]. The tumor-associated prothrombotic state contributes to the process of tumor dissemination and growth. Therefore, tumor growth and metastasis formation are connected with higher frequency of VTE events [23, 24, 30, 33, 34, 46].

## Conclusions

Concomitant history of cancer in acute PE was associated with higher PE severity status and therefore poorer outcome.

## Limitations and strength

Our study has several limitations. Data quality is reduced due to the study design (single center, retrospective data analysis). The single-center study design study in a larger general hospital of basic and regular medical care could lead to a selection bias. Severe PE cases and younger PE patients could be taken to specialist units of university medical center (chest pain unit), which is located in the nearer surrounding in the same city. We did not assess further co-morbidities than the presented ones. This will be the subject of further examinations. Moreover we did not assess the cancer types and stages and therapeutic differences of the enrolled patients. This is a major limitation of this study.

## Authors' contributionss/Wkład autorów

KK – study design, data collection and interpretation, statistical analysis, manuscript preparation, literature search. MG, JB, MC, JOB, WD – study design, data collection and interpretation, manuscript preparation, literature search.

## Conflict of interest/Konflikt interesu

None declared.

## Financial support/Finansowanie

None declared.

## Ethics/Etyka

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

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All authors have conceptualised the study design and took part in writing of the manuscript. All authors have read the last version of the manuscript and approved the submission.

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