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Syncope in the German Nationwide inpatient sample – Syncope in atrial fibrillation/flutter is related to pulmonary embolism and is accompanied by higher in-hospital mortality

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ABSTRACT

Aims: Syncope is a common phenomenon in the general population. Although most of the causes are of benign origin, some comorbidities are accompanied by high mortality.

We aimed to compare the in-hospital mortality of patients with syncope related to different comorbities and investigate the impact of syncope in patients with atrial fibrillation/flutter (AF).

Methods: The nationwide inpatient sample of Germany of the years 2011–2014 was used for this analysis. Patients with syncope (ICD-code R55) were stratified by presence of selected comorbidities. Additionally, AF patients with and without syncope were compared. Incidence of syncope and in-hospital mortality were calculated. Syncope as a predictor of adverse outcome in AF patients was investigated.

Results: In total, 1,628,859 hospitalizations of patients with syncope were identified; incidence was 504.6/100,000 citizens/year with case-fatality rate of 1.6%. Patients with syncope revealed frequently comorbidities as AF, heart failure and pneumonia. In-hospital mortality was high in syncope patients with pulmonary embolism (PE, 13.0%), pneumonia (12.8%), myocardial infarction (MI, 9.7%) and stroke (8.5%).

We analysed 1,106,019 hospitalizations (52.9% females, 54.9% aged > 70 years) of patients with AF (2011–2014). Among these, 23,694 (2.1%) were coded with syncope and 0.7% died. Syncope had no significant impact on in-hospital mortality (OR 1.04, 95%CI 0.92–1.17, $P = .503$) independently of age, sex and comorbidities, but was associated with PE (OR 1.83, 95%CI 1.42–2.36, $P < .001$), MI (OR 1.68, 95%CI 1.48–1.90, $P < .001$), stroke (OR 1.66, 95%CI 1.42–1.94, $P < .001$) and pneumonia (OR 1.26, 95%CI 1.16–1.37, $P < .001$).

Conclusions: Syncope is a frequent cause for referrals in hospitals. While the overall in-hospital mortality rate is low (< 2%), syncope in coprevalence with PE, pneumonia, MI and stroke showed a mortality rate > 8%. Syncope in AF patients had no independent impact on in-hospital mortality.

1. Introduction

Syncope is a common phenomenon during life-time in the general population and is a frequent cause for patients' referral at emergency departments [1–6]. Syncope is defined as a transient loss of consciousness caused by transient global cerebral hypoperfusion [2,7,8]. A syncope is characterized by a rapid onset, a short duration, and is followed by a spontaneous complete recovery [2,7,8]. It occurs often without warning and an exact duration of unconsciousness could only rarely estimated [2,7,8]. It has to be differentiated from transient loss of consciousness due to other disorders for example epileptic seizures, trauma, psychiatric causes or provoked unconsciousness by noxes like alcohol or other drugs [2,7–11].

According to the current classification recommended by the ESC guidelines [2], syncope can be neurally caused (i.e., vasovagal, situational, orcarotid-sinus syndrome, non-classical forms), mediated by orthostatic hypotension (i.e., drug-induced, due to primary or secondary autonomic failure or due to volume depletion), or could have a

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cardiovascular origin (including arrhythmias, structural cardiovascular diseases, or pulmonary embolism (PE)) [2,7,8,12,13].

While most potential causes of syncope are of benign origin and often self-limited, other etiologies are related to significant morbidity and mortality [5,8,12,13]. Only in approximately 2/3 of the patients the reason underlying the syncope could be identified [14]. The most prevalent causes for syncope are vasovagal in 21.2%, cardio-vascular in 9.5%, and orthostatic in 9.4% reasons [14]. Life-threatening causes are predominantly based on cardio-vascular diseases and bleeding events [5].

Thus, we aimed (1st) to investigate the incidence of syncope in hospitalized patients in Germany, (2nd) to compare the incidences of syncope stratified for sex and specific comorbidities, (3rd) to explore the relative in-hospital mortality of syncope in generall as well as with and without these specific comorbidities and (4th) to investigate the impact of syncope on outcomes in patients with atrial fibriallation/flutter (AF).

2. Methods and patients

For this analysis, the nationwide German inpatient sample (diagnosis related groups (DRG) statistic) was used. The nationwide inpatient sample consists of treatment, diagnostic and procedural/surgical data from all hospitalized patients in Germany and all cases are coded according to the DRG system. In Germany, diagnoses of inpatients are coded according to ICD-10-GM (International Classification of Diseases, 10th Revision with German Modification) and diagnostic, surgical or interventional procedures with OPS codes (Operationen- und Prozedurenschlüssel). All DRG diagnoses of inpatients are collected and evaluated by the Federal Statistical Office of Germany (Statistisches Bundesamt).

Firstly, we requested the total numbers of hospitalizations of patients diagnosed with syncope (ICD code R55) of the years 2011–2014 from the Federal Statistical Office of Germany (Statistisches Bundesamt, DEStatis, source: DRG-Statistik, Sonderauswertung des Statistischen Bundesamtes).

Patients with syncope were stratified for the presence of important comorbidities, which might be related to the development of syncope, such as AF (ICD code I48), heart failure (HF; ICD code I50), pneumonia, iron deficiency anaemia (ICD code D50), sick-sinus-syndrome (ICD code I49.5), myocardial infarction (MI; ICD code I21 (not including recurrent MI events during the first months (ICD code I22))), stroke (ICD codes I61-I64), vestibular impairment/failure (ICD code H81), deep venous thrombosis or thrombophlebitis (DVT; ICD code I80), PE (ICD code I26), pacemaker or implantable cardioverter defibrillator malfunction (ICD code T82.1), meningioma (ICD code D32), carotid sinus syndrome (ICD code G90.00), and ventricular tachycardia caused by re-entry tachycardia (ICD code I47.0). In addition, the number of in-hospital deaths in these syncope patients with the mentioned comorbidities was requested.

Secondly, for further analysis (included in the second part of the study), we focused on patients with AF and compared AF patients with and without syncope in the German nationwide inpatient sample between 2011 and 2014. The analyses were performed on our behalf by the Research Data Center of the Federal Statistical Office and the Statistical Offices of the federal states in Wiesbaden, Germany (source: RDC of the Federal Statistical Office and the Statistical Offices of the federal states, DRG Statistics 2005–2015, own calculations). The aggregated statistical results were analysed with the help of SPSS codes (SPSS® software, version 20.0, SPSS Inc., Chicago, Illinois), which were sent by us to the Research Data Center. Regarding this analysis, we selected all inpatients who were coded with a main diagnosis of AF between 2011 and 2014. Patients' main diagnosis is defined as the diagnosis, which is mainly responsible for patients' hospitalization [15].

2.1. Definitions

Syncope was defined as transient loss of consciousness due to transient global cerebral hypoperfusion according to the ESC guidelines as the current guidelines used in clinical practice in Europe [2,8]. Pneumonia (ICD codes J12-J18) comprised both virus as well as bacterial pneumoniae. Stroke diagnosis included ischemic as well as haemorrhagic stroke.

2.2. Study outcome

The primary outcome of this study was death of all-causes during in-hospital stay (in-hospital death). In addition, for the second part of this study, adverse in-hospital event was defined as a composite of all-cause in-hospital death, mechanical ventilation (MV, OPS codes 8–70 and 8–71), or cardio-pulmonary resuscitation (CPR, OPS code 8–77).

2.3. Ethical aspects

Because this study did not involve direct access by the investigators to data on individual patients but only access to summary results provided by the Research Data Center, approval by an ethics committee and informed consent were not required, in accordance with German law.

2.4. Statistical analysis

The descriptive statistical data comprise the total numbers of inpatients diagnosed with syncope singularly and with the additional mentioned comorbidities, as well as the in-hospital deaths. We calculated the incidence of syncope and of syncope with the mentioned comorbidities in Germany and the relative in-hospital mortality rates. The annual incidence was calculated as the total number of syncopes per 100,000 citizens of the German population. In addition, we stratified the numbers of hospitalizations of patients with syncope according to different age-groups.

For further analysis in the second part of the study focussing on patients with AF, we compared AF patients with and without syncope. Descriptive statistics for baseline comparisons were provided as median and interquartile range (IQR), or as absolute numbers and corresponding percentages. We tested the continuous variables using the Mann-Whitney-*U* test and categorical variables with Fisher's exact or chi-square test, as appropriate.

Univariate and multivariate logistic regression models were analysed to investigate the impact of syncope on in-hospital events (DVT, PE, pneumonia, stroke and MI) as well as on the in-hospital mortality. Additionally, the impact of DVT, PE, pneumonia, stroke and MI on in-hospital death in AF patients with syncope was analysed in univariate and multivariate regression models. Results were presented as Odds Ratios (OR) and corresponding 95% CI. Multivariate logistic regression models, testing the independence of predictors for in-hospital events and mortality, were adjusted either I) for age and sex or II) for age, sex, obesity (ICD code E66), cancer (ICD codes C00-C97), HF, essential arterial hypertension (ICD-code I10), renal insufficiency (comprised diagnosis of chronic renal insufficiency stages three to five with glomerular filtration rate $< 60\,ml/min/1{,}73\,m^2$, ICD codes N18.3, N18.4 and N18.5), diabetes mellitus (ICD-codes E10-E14), peripheral artery disease (ICD code I70.2), coronary artery disease (ICD code I25), chronic obstructive pulmonary disease (COPD, ICD code J44).

The software SPSS® (version 20.0; SPSS Inc., Chicago, Illinois) was used for computerised analysis. P values of < 0.05 (two-sided) were considered to be statistically significant.

3. Results

Overall, 1,628,859 hospitalizations of patients were diagnosed with

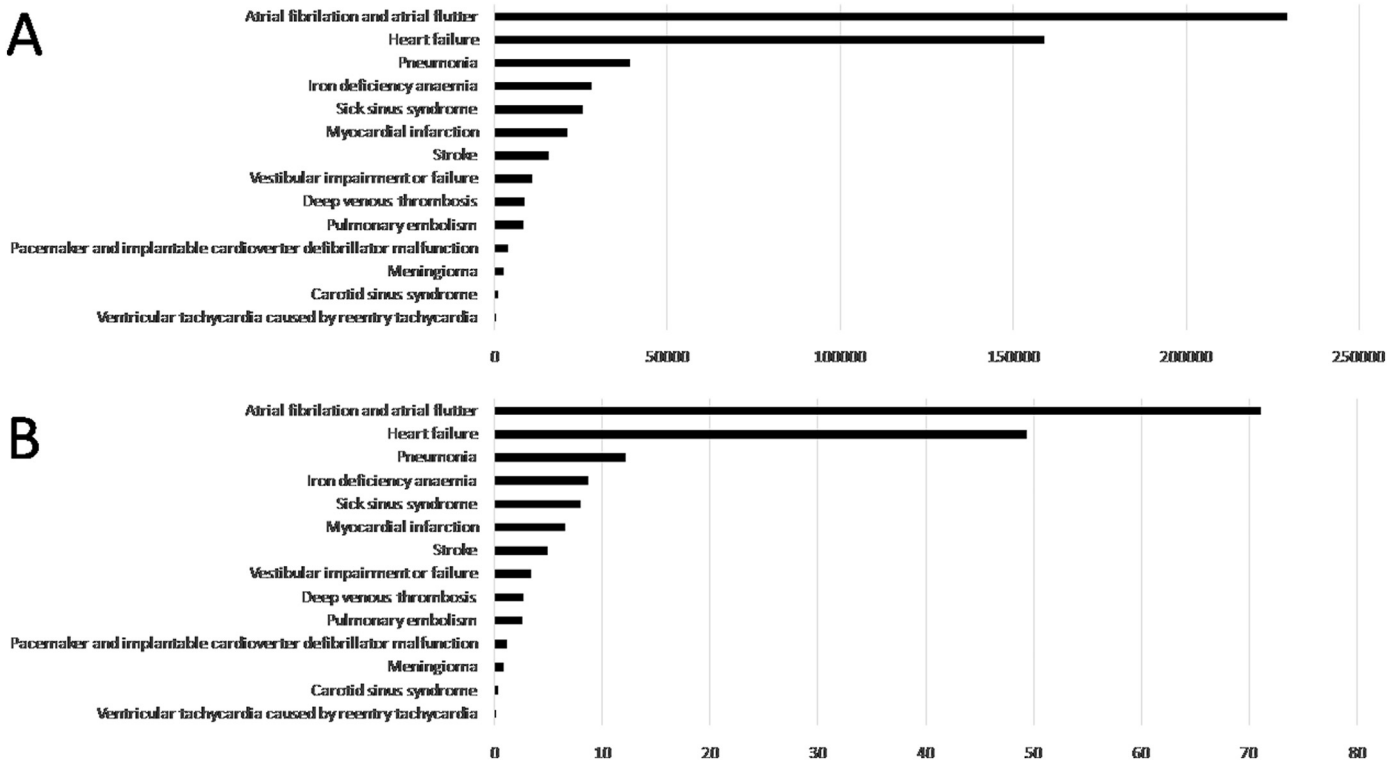

Fig. 1. Absolute numbers of hospitalized patients with syncope (A) and incidence of syncope in Germany per year in hospitalized patients (B).

syncope in Germany between the years 2011 and 2014. The incidence of syncope was 504.6 hospitalized cases per 100,000 citizens in Germany per year.

The absolute numbers of hospitalizations of patients with syncope revealed frequently comorbidities as AF, HF, pneumonia, iron deficiency aneamia, sick-sinus-syndrome, MI and stroke. The incidence of syncope in coprevalence with the mentioned comorbidirties was highest in AF with 71.0, HF 49.3 and pneumonia 12.1 hospitalized patients per 100,000 citizens in Germany per year (Fig. 1).

In contrast, lowest incidence of hospitalized syncope patients in coprevalence with the investigated comorbidities was detected in syncope patients with ventricular tachycardia caused by reentry tachycardia 0.1, carotid sinus syndrome 0.3, meningioma 0.8, pacemaker and implantable cardioverter defibrillator malfunction 1.2, PE 2.6 and DVT 2.7 hospitalized cases per 100,000 citizens in Germany per year (Fig. 1).

The absolute numbers and the incidence of hospitalizations for syncopes increased markedly with growing age (Fig. 2).

The case-fatality rate of all syncope patients in Germany was low (1.6%). While the slight majority of the patients with syncope event were of female gender (54.5%), the in-hospital mortality was higher in males (1.9% vs. 1.4%).

The in-hospital mortality rate was high in syncope patients with PE (13.0%), pneumonia (12.8%), MI (9.7%), stroke (8.5%), and DVT (3.9%). In contrast, syncope patients with additional diagnoses of ventricular tachycardia caused by reentry tachycardia, carotid sinus syndrome, and vestibular impairment/failure revealed a low in-hospital mortality of < 1% (Fig. 3).

AF was the most prevalent comorbidity of hospitalized patients with syncope in our investigation. Thus, for further analysis, we focused on patients with AF and compared AF patients with and without syncope. Overall, 1,106,019 patients (49.0% females, 77.3% aged > 70 years) were admitted to German hospitals for AF between 2011 and 2014. Among these 23,694 (2.1%) were coded with syncope. AF patients revealed the following rates of AF subtypes: 34.2% had a paroxysmal, 61.3% a persisting and 4.5% a long-standing persisting (formaly known as permanent) AF.

In total, 7872 (0.7%) inpatients died, 25,690 (2.3%) revealed an adverse in-hospital event, 6051 (0.5%) had a myocardial infarction and 3473 (0.3%) had to undergo CPR during in-hospital course.

AF patients with syncope were older (77 (70–83) vs. 72 (63–78) years, $P < .001$) and particularly long-standing persisting AF was more prevalent in AF patients with syncope than in those without (7.7% vs. 4.0%, $P < .001$); both other AF sybtypes were more often found in AF patients without syncope (Table 1). AF patients with syncope revealed more often cardiovascular diseases as well as cancer (2.7% vs. 1.6%, $P < .001$) and renal insufficiency was distinctly more frequently coded in AF patients with syncope in comparison to those without (23.2% vs. 14.9%, $P < .001$). In contrast, patients without syncope were more often obese (8.1% vs. 5.5%, $P < .001$) and had more frequently essential arterial hypertension (56.5% vs. 54.6%, $P < .001$) (Table 1).

The outcomes all-cause in-hospital death (1.2% vs. 0.7%, $P < .001$) and adverse in-hospital events (3.0% vs. 2.3%, $P < .001$) as well as CPR (0.8% vs. 0.3%, $P < .001$) were more frequent in AF patients with syncope. Consistently, the comorbidities/conditions pneumonia (2.8% vs. 1.7%, $P < .001$), venous thromboembolism (0.7% vs. 0.4%, $P < .001$) with the entity PE (0.3% vs. 0.1%, $P < .001$) and high-risk PE (defined as PE event with haemodynamically instability [comprising shock, MV and/or CPR], 0.04% vs. 0.01%, $P = .001$), and MI (1.1% vs. 0.5%, $P < .001$) showed higher prevalence in AF patients with than without syncope (Table 1). Also bleeding events such as intracerebral bleeding (0.06% vs. 0.03%, $P = .006$), subarachnoid bleeding (0.03% vs. 0.01%, $P < .001$) as well as gastrointestinal bleeding (0.6% vs. 0.2%, $P < .001$ and the need for transfusion of blood constituents (2.4% vs. 0.9%, $P < .001$) were more often in AF patients with syncope (Table 1).

While syncope had no significant impact on in-hospital mortality (OR 1.04, 95%CI 0.92–1.17, $P = .503$) independently of age, sex and comorbidities, presence of syncope in AF patients was associated with an elevated risk for the occurrence of PE (OR 1.83, 95%CI 1.42–2.36, $P < .001$), MI (OR 1.68, 95%CI 1.48–1.90, $P < .001$), stroke (OR 1.66, 95%CI 1.42–1.94, $P < .001$) and pneumonia (OR 1.26, 95%CI

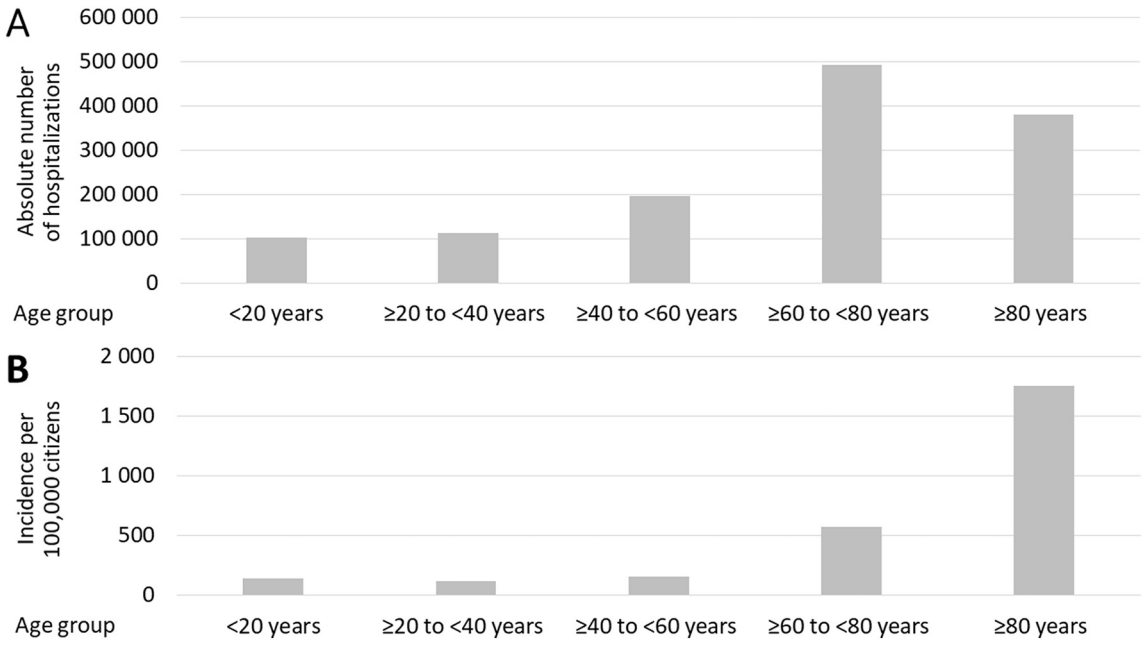

Fig. 2. Absolute numbers (A) and incidence (B) of hospitalizations of patients with syncope stratified for age groups.

1.16–1.37, $P < .001$) (Table 2).

PE, MI, pneumonia and stroke had a strong impact on the in-hospital mortality of AF patients with syncope independently of age, sex and comorbidities (Table 3).

4. Discussion

Syncope is a common symptom in patients presenting at emergency rooms and the presence of syncope is challenging for initial medical evaluation due to the complexity of the disorder and the wide spectrum from benign to acute life-threatening underlying causes [2,14,16,17].

The key results of our study analyzing the nationwide German in-patients comprise the following points:

i) The incidence of syncope in hospitalized patients was high with 504.6 cases per 100,000 citizens in Germany per year.
ii) Syncopes were more prevalent in older age.
iii) AF, HF and pneumonia are common comorbidities in syncope patients.
iv) In-hospital case-fatality rate of all syncope patients in Germany was low with 1.6%.
v) The in-hospital mortality rate was high in syncope patients with PE (13.0%), pneumonia (12.8%), MI (9.7%) and stroke (8.5%).
vi) Syncope patients with coprevalence carotid sinus syndrome and vestibular impairment/failure showed a low in-hospital mortality (< 1%).
vii) AF patients with syncope had a significant higher in-hospital mortality rate than those AF patients without (1.2% vs. 0.7%).

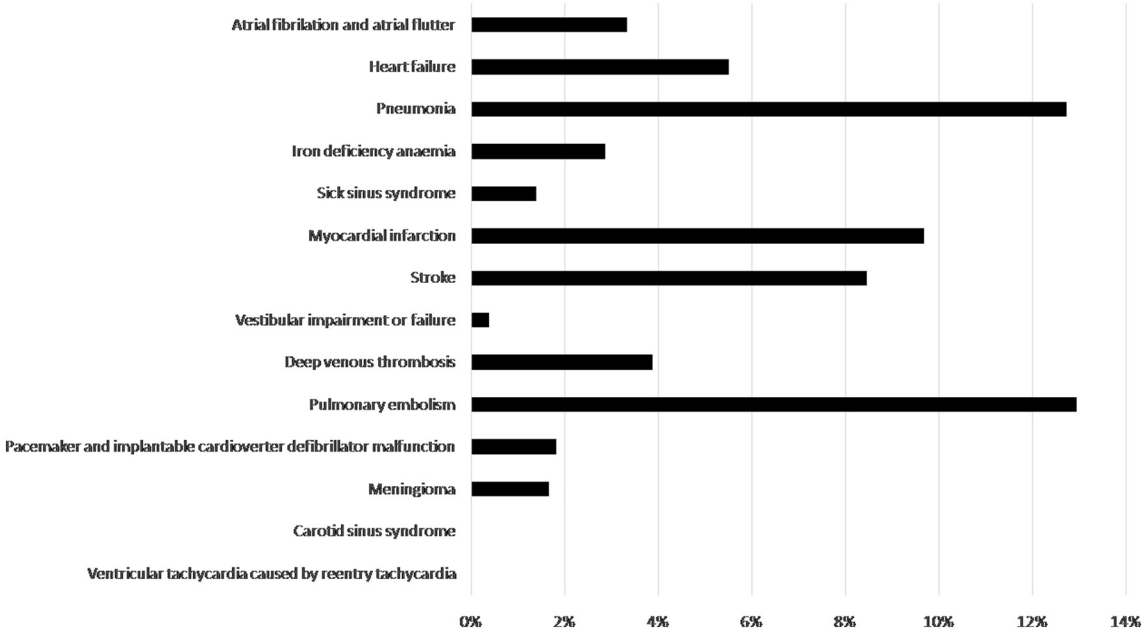

Fig. 3. Case-fatality rate during in-hospital stay in patients with coded syncope stratified for important comorbidities that might be related to the development of syncope.

Table 1
Patient characteristics and comorbid conditions of the 1,106,019 AF patients with and without syncope.

Parameters	AF patients with syncope	AF patients without syncope	*P*-value
	n = 23,694 (2.1%)	*n* = 1,082,325 (97.9%)	
Age (years)	77 (70–83)	72 (63–78)	< .001
Age > 70 years	17,624 (74.4%)	589,993 (54.5%)	< .001
Female sex[a]	12,526 (52.9%)	514,154 (47.5%)	< .001
In-hospital stay (days)	7 (4–10)	4 (2–7)	< .001
Obesity	1310 (5.5%)	87,998 (8.1%)	< .001
Atrial fibrillation			
Paroxysmal AF	7196 (30.4%)	340,916 (31.5%)	< .001
Persisting AF	13,158 (55.5%)	609,971 (56.4%)	.011
Long standing persisting (permanent) AF	1820 (7.7%)	43,720 (4.0%)	< .001
Comorbidities			
Cancer	648 (2.7%)	17,687 (1.6%)	< .001
Coronary artery disease	5574 (23.5%)	249,517 (23.1%)	.089
Chronic (left) heart failure	5295 (22.3%)	226,803 (21.0%)	< .001
Peripheral artery disease	653 (2.8%)	20,353 (1.9%)	< .001
Chronic obstructive pulmonary disease	1521 (6.4%)	63,595 (5.9%)	< .001
Essential arterial hypertension	12,932 (54.6%)	611,464 (56.5%)	< .001
Renal insufficiency	5487 (23.2%)	161,433 (14.9%)	< .001
Diabetes mellitus	5102 (21.5%)	200,223 (18.5%)	< .001
Coagulation abnormalities	1217 (5.1%)	28,694 (2.7%)	< .001
Thrombophilia	22 (0.09%)	884 (0.08%)	.552
Potential life-threatening conditions			
Pneumonia	660 (2.8%)	18,312 (1.7%)	< .001
Venous thromboemebolism	166 (0.7%)	4840 (0.4%)	< .001
Deep vein thrombosis or thrombophlebitis	117 (0.5%)	3846 (0.4%)	< .001
Pulmonary embolism	63 (0.3%)	1240 (0.1%)	< .001
Pulmonary embolism – High risk status	9 (0.04%)	114 (0.01%)	.001
Fatal pulmonary embolism	4 (0.02%)	87 (0.01%)	.132
Shock	123 (0.5%)	2773 (0.3%)	< .001
Mechanical ventilation	388 (1.6%)	18,410 (1.7%)	.455
Cardio-pulmonary resuscitation	190 (0.8%)	3283 (0.3%)	< .001
Myocardial infarction	259 (1.1%)	5792 (0.5%)	< .001
Intracerebral bleeding	14 (0.06%)	271 (0.03%)	.006
Subarachnoid bleeding	7 (0.03%)	52 (0.01%)	< .001
Gastro-intestinal bleeding	140 (0.6%)	2838 (0.2%)	< .001
Transfusion of blood constituents	568 (2.4%)	10,053 (0.9%)	< .001
Primary and secondary study outcome			
Adverse in-hospital events	710 (3.0%)	24,980 (2.3%)	< .001
All cause in-hospital death	295 (1.2%)	7577 (0.7%)	< .001

[a] Data available for 1,105,993 patients.

viii) Syncope had no significant impact on the risk to die during in-hospital stay independently of age, sex and comorbidities.
ix) Syncope in AF patients was an independent predictor for occurrence of PE, MI, pneumonia and stroke.
x) PE, MI, pneumonia and stroke were independent predictors of in-hospital death in AF patients with syncope

Syncope is a common phenomenon in the general population [1,2]. Up to 1/3 of the general population develop at least one syncope during life-time [1,3,4] and between 1% and 3% of referrals at the emergency departments are due to syncopes [2,4–6,17]. Studies reported an annual incidence of 6200 to 39,700 per 100,000 citizens with a significant age-dependent increase of the syncope incidence after the 70th life-year [14,18]. The incidence of syncope in the hospitalized cohort of our study was distinctly lower compared to the mentioned numbers above driven by our focus on hospitalized patients in the present study in contrary to the other studies evaluating syncope incidence in the general population. However, the incidence of 504.6 cases in hospitalized patients per 100,000 citizens in Germany (of our study) was only slightly lower than the reported 800 to 930 syncope events in hospitalized patients per 100,000 citizens in the United States of America per year reported by Alshekhlee et al. [19]. As expected, incidence of syncope increased substantially with age.

The in-hospital case-fatality rate of all syncope patients in Germany was 1.6% and therefore higher than the reported rate of 0.3% in the study of Alshekhlee et al. [19]. In accordance with the the study of Alshekhlee et al. [19] the overall mortality in our study was slightly higher in male patients with syncope in comparison to females, whereas Soteriades et al. [14] found an equal incidence of the incidence of syncope in male and female individuals. While the overall in-hospital mortality rate of syncope patients without cardiovascular comorbidites was low in our study, syncope patients with cardiovascular comorbidities revealed a high in-hospital mortality rate.

The most prevalent comorbidities in combination with syncope in our study were AF, HF or pneumonia. AF and syncope are both common diseases in the general population with multifactorial etiology. Our study showed higher percentage (14.1%) of syncope patients affected by AF than other studies (2.7% arrhythmia in syncope patients) [19]. AF seems to be a trigger for syncope [20,21]. Syncope in AF patients as a result of an interruption of cerebral blood flow can be induced by rapid ventricular or bradycardia episodes as well as an abnormal cardioinhibitory response resulting in a vasovagal syncope [20–23]. In our study 1.4% of the syncope patients had a sick sinus syndrome, whereas 0.01% of these patients were diagnosed with ventricular tachycardia caused by reentry tachycardia. AF associated with the Wolf-Parkinson-White (WPW) syndrome can lead to rapid ventricular rates, causing syncope [22]. More than half of the patients with sick sinus syndrome have a bradycardia-tachycardia syndrome, usually manifesting as sinus bradycardia alternating with paroxysmal atrial tachycardia or AF.

Table 2
Univariate and adjusted multivariate logistic regression models for syncope predicting different potential life-threatening conditions and in-hospital mortality in AF patients.

Syncope predicting	Univariate logistic regression analysis[a]	Multivariate logistic regression analysis[b]	Multivariate logistic regression analysis[c]
In-hospital death	OR 1.79, 95%CI 1.59–2.01, *P* < .001	OR 1.07, 95%CI 0.95–1.20, *P* = .275	OR 1.04, 95%CI 0.92–1.17, *P* = .503
DVT	OR 1.39, 95%CI 1.16–1.67, *P* < .001	OR 1.20, 95%CI 1.00–1.44, *P* = .054	OR 1.19, 95%CI 0.99–1.44, *P* = .060
PE	OR 2.32, 95%CI 1.80–3.00, *P* < .001	OR 1.88, 95%CI 1.46–2.43, *P* < .001	OR 1.83, 95%CI 1.42–2.36, *P* < .001
Pneumonia	OR 1.66, 95%CI 1.53–1.79, *P* < .001	OR 1.25, 95%CI 1.15–1.35, *P* < .001	OR 1.25, 95%CI 1.16–1.36, *P* < .001
Myocardial infarction	OR 2.05, 95%CI 1.81–2.33, *P* < .001	OR 1.61, 95%CI 1.42–1.82, *P* < .001	OR 1.68, 95%CI 1.48–1.90, *P* < .001
Stroke	OR 2.11, 95%CI 1.81–2.46, *P* < .001	OR 1.68, 95%CI 1.44–1.96, *P* < .001	OR 1.66, 95%CI 1.42–1.94, *P* < .001

Abbreviations: OR, indicates for odds ratio; CI, confidence interval; PE, pulmonary embolism; DVT, deep venous thrombosis.
[a] Not adjusted.
[b] Adjusted for age and sex.
[c] Adjusted for age, sex, obesity, cancer, heart failure, essential arterial hypertension, renal insufficiency, diabetes mellitus, peripheral artery disease, coronary artery disease, chronic obstructive pulmonary disease.

Table 3
Univariate and adjusted multivariate logistic regression models for potential life-threatening conditions predicting in-hospital death in AF patients with syncope.

	Univariate logistic regression analysis[a]	Multivariate logistic regression analysis[b]	Multivariate logistic regression analysis[c]
DVT	OR 1.38, 95%CI 0.34–5.62, $P = .651$	OR 1.26, 95%CI 0.31–5.14, $P = .751$	OR 0.94, 95%CI 0.23–3.86, $P = .930$
PE	OR 8.50, 95%CI 3.64–19.88, $P < .001$	OR 7.95, 95%CI 3.34–18.90, $P < .001$	OR 6.83, 95%CI 2.81–16.62, $P < .001$
Pneumonia	OR 11.78, 95%CI 8.89–15.62, $P < .001$	OR 9.26, 95%CI 6.95–12.34, $P < .001$	OR 6.43, 95%CI 4.76–8.68, $P < .001$
Myocardial infarction	OR 8.73, 95%CI 5.64–13.51, $P < .001$	OR 6.80, 95%CI 4.37–10.60, $P < .001$	OR 5.35, 95%CI 3.36–8.51, $P < .001$
Stroke	OR 6.28, 95%CI 3.45–11.42, $P < .001$	OR 6.40, 95%CI 3.48–11.75, $P < .001$	OR 6.16, 95%CI 3.28–11.54, $P < .001$

Abbreviations: OR, indicates for odds ratio; CI, confidence interval; PE, pulmonary embolism; DVT, deep venous thrombosis.
[a] Not adjusted.
[b] Adjusted for age and sex.
[c] Adjusted for age, sex, obesity, cancer, heart failure, essential arterial hypertension, renal insufficiency, diabetes mellitus, peripheral artery disease, coronary artery disease, chronic obstructive pulmonary disease.

These patients may experience syncope from sinus arrest or following spontaneous conversion from a supraventricular tachycardia to sinus rhythm with a long sinus node pause [22]. Interruption of cerebral blood flow for 8–10 s usually produces a loss of consciousness [23]. Although, it is well-established that ventricular tachycardia in connection with reentry substrates are commonly based on structural heart disease and associated with an increased risk of sudden death [24–26], our study showed unexpectingly a low in-hospital mortality rate in these patients with syncope and ventricular tachycardia caused by reentry tachycardia. This low in-hospital mortality might be based on an underreporting/undercoding of such an arrhythmia in context of structural heart diseases (MI and HF), an underdetection of this arrhythmia as the primary cause of sudden in-hospital death or the sudden death occurred already outside the hospital and the patient did not reached the hospital alive.

The present study demonstrated in accordance with the literature that AF and syncope both are common disease entities with a significant coprevalence [20,27]. Our results revealed a higher in-hospital mortality rate in AF patients with syncope compared to those without syncope (1.2% vs. 0.7%, $P < .001$). Consistingly, the risk for adverse in-hospital events was higher in AF patients with syncope compared to those without independently of age, sex and comorbidities. These findings are in line with the literature showing that cardiovascular syncope (including arrhythmias) is well known to be associated with an increased short-term mortality [5]. However, some studies reported that AF is an unusual and rare cause of syncope [20,27]. Although the univariate logistic regression model confirmed that syncope was a predictor of in-hospital death, the multivariate regression models demonstrated that syncope had no significant impact on the risk to die during in-hospital stay, if the multivariate model was adjusted for age, sex and comorbidities. Therefore, syncope was not an independent predictor for in-hospital mortality in AF patients. In contrast, syncope was associated with occurrence of PE, myocardial infarction, pneumonia and stroke in AF patients. The risk of these important triggers of in-hospital mortality were independently elevated by presence of syncope in AF patients and PE, myocardial infarction, pneumonia and stroke were independent predictors of in-hospital death in AF patients with syncope. Regarding stroke, syncope might be the result or first sign of the stroke event itself especially if stroke or precursory transient ischemic attack were not directly or adequately diagnosed. Another explanation might be that paroxysmal AF patients experience syncope from spontaneous conversion from a supraventricular tachycardia to sinus rhythm with a long sinus node pause or sinus arrest in AF patient with sick sinus syndrome [22,23]. Beside the syncope due to interruption of cerebral blood flow, in parallel thrombi in the left atrial appendage might break loose and travel to the brain resulting in stroke [28–30].

Of note, the analysed data of the nationwide sample could not provide information about pathomechanisms, but only about coprevalences, nevertheless the high coprevalence of AF and syncope seems noticeable.

Syncope patients with additional diagnoses of carotid sinus syndrome and vestibular impairment/failure showed a low in-hospital mortality rate of < 1% in our analysis. This is partly in accordance with the literature showing a favourable outcome for both of the most common pathomechanism (vasovagal syncope and not-cardiovascular syncopes) [14,17].

Overall, 9.8% of the syncope patients in the present study had a comorbidity of HF and 1.3% of MI. Although comparative data in this context are sparse, in the literature 12% of the patients with severe HF had a syncope [31]. Syncope patients with advanced heart failure are at high risk for sudden death regardless of the etiology of syncope; however, the risk for sudden death is primarily elevated by ventricular arrhythmias [31,32]. The most frequent causes for syncope in patients with HF and MI are arrhythmias due to decreased cardiac output, haemodynamic impairment and subsequent decrease in cerebral blood flow [23]; approximately ¾ of these patients had ventricular tachyarrhythmias, supraventricular tachycardia or orthostatic hypotension leading to syncope events [31]. In particular, MI patients are prone to develop cardio-neuromediated reactions with sympathetic withdrawal [33]. Remarkably, presence of syncope during an episode in acute coronary syndrome and in MI is commonly caused by severe myocardial ischemia due to an acute vascular occlusion [34]. Syncope in MI patients revealed high in-hospital mortality (9.7%) in the German nationwide inpatient sample.

Inpatients with other cardiovascular causes such as stroke, PE and DVT, showed frequencies of 0.9%, 0.5% and 0.5% in the syncope patients, respectively. All of these frequencies in syncope patients were slightly higher than in the study of Alshekhlee et al. [19]. Syncope in DVT might be predominantly driven by undiagnosed/overlooked PE. Syncope in patients with PE (13.0%) and stroke (8.5%), demonstrated high in-hospital mortality in the German nationwide inpatient sample. It was hypothesized that syncope in acute PE might be primarily caused by large pulmonary artery embolus with extensive occlusions in the pulmonary vascular tree accompanied by right ventricular dysfunction (RVD) or triggered by vasovagal reflex (Bezold-Jarisch reflex). Both pathomechanisms are leading to a sudden impaired left ventricular filling followed by a reduction in cardiac output with arterial hypotension, reduced cerebral blood flow and result in syncope/collapse [13,35–42]. Additionally, RVD and hyoxemia may increase the risk for arrhythmias with concomitant syncope [13,35,37,38,40,43,44]. Our study did not differentiate between hemodynamically stable and unstable PE patients regarding the in-hospital mortality in all syncope patients with PE; syncope in unstable PE patients might be attended by distinctly higher mortality than in hemodynamically stable PE patients [45]. Remarkably, syncope was in our study also an independent predictor for occurrence of PE in AF patients in the fully adjusted multivariate model.

Thus, syncope events caused by cardiovascular diseases or occurring in coprevalence with cardiovascular diseases revealed a high in-hospital motrtality and syncope events in these patients should increase the awareness and trigger a special attention of the physicians on these

high-risk patients in the emergency departments. Cardiovascular syncope should result in better monitoring and these patients might be a target group for more aggressive treatments [14,34,46,47]. Particularly in AF patients, syncope should rise the awareness for impending or already occurred cardiovascular events such as PE, MI and stroke, but also pneumonia. Especially patients with cerebrovascular syncope, represent a high-risk population and had in accordance with the literature a limited prognosis [14,17].

Syncope in pneumonia was observed in 2.4% of our patients. In accordance, Chen et al. [48] reported that syncope and falls are prevalent in > 3% of the old patients with pneumonia [48]. Syncope in patients with pneumonia revealed high in-hospital mortality (12.8%) in the German nationwide inpatients sample. Pathomechanism of syncope in pneumonia patients comprise on the one hand progressive confusion culminating in loss of consciousness and hypotension due to infection and on the other hand cough syncopes [2,49]. In some of the patients, pneumonia is the consequence of PE after hypoperfusion and pulmonary infarction.

4.1. Limitations

There are some limitations that require consideration: Our study results are based on ICD and OPS discharge codes of hospitalized patients. This could lead to incomplete data due to under-reporting/under-coding. In order to encounter this linitations, the focus of our study was on clear endpoints/clinical conditions, such as in-hospital mortality and PE, MI stroke, CPR and pneumonia, which are very unlikely to be miscoded or not coded. This study includes in-hospital results only and cannot address long-term outcomes.

5. Conclusions

Syncope is a frequent cause for referrals in the hospitals. The incidence of syncope in hospitalized patients was high with 504.6 cases per 100,000 citizens in Germany per year. While the overall in-hospital mortality was low with 1.6%, syncope in coprevalence with PE, pneumonia, MI and stroke showed a mortality rate > 8%. Syncopes were more prevalent in older age and particularly, AF is a common comorbidity in patients with syncope. AF patients with syncope had a significant higher in-hospital mortality rate than those without (1.2% vs. 0.7%), but syncope had no significant impact on the risk to die during in-hospital stay independently of age, sex and comorbidities. Syncope in AF patients was an independent predictor for the occurrence of PE, MI, pneumonia and stroke.

Thus, patients with syncope events caused by cardiovascular diseases or occurring in coprevalence with cardiovascular diseases should be monitored more closely and these patients might be a target group for more aggressive treatments.

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Conflict of interest

The authors have no conflict of interests with this article.

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References

[1] Weber T. Stellenwert der Kipptischuntersuchung in der Synkopenabklärung. Aust J Cardiol 2003;10:473–80.
[2] Moya A, Sutton R, Ammirati F, Blanc JJ, Brignole M, Dahm JB, et al. Guidelines for the diagnosis and management of syncope (version 2009). Eur Heart J 2009;30:2631–71.
[3] Savage DD, Corwin L, McGee DL, Kannel WB, Wolf PA. Epidemiologic features of isolated syncope: the Framingham study. Stroke 1985;16:626–9.
[4] Shukla GJ, Zimetbaum PJ. Cardiology patient page. Syncope Circ 2006;113:e715–7.
[5] Lemonick DM. Evaluation of syncope in the emergency department. Am J Clin Med 2010;7:11–9.
[6] Miller TH, Kruse JE. Evaluation of syncope. Am Fam Physician 2005;72:1492–500.
[7] Strickberger SA, Benson DW, Biaggioni I, Callans DJ, Cohen MI, Ellenbogen KA, et al. AHA/ACCF scientific statement on the evaluation of syncope: from the American Heart Association councils on clinical cardiology, cardiovascular nursing, cardiovascular disease in the young, and stroke, and the quality of care and outcomes research interdisciplinary working group; and the American College of Cardiology Foundation in collaboration with the Heart Rhythm Society. J Am Coll Cardiol 2006;47:473–84.
[8] Brignole M, Moya A, de Lange FJ, Deharo JC, Elliott PM, Fanciulli A, et al. 2018 ESC guidelines for the diagnosis and management of syncope. Eur Heart J 2018;39:1883–948.
[9] Lee H, Roh S, Kim DJ. Alcohol-induced blackout. Int J Environ Res Public Health 2009;6:2783–92.
[10] Stell JM, Ryan JM. Ecstasy and neurodegeneration. Gamma-Hydroxybutyrate is a new recreational drug that may lead to loss of consciousness. BMJ 1996;313:424.
[11] O'Brien M, Nutt D. Loss of consciousness and post-traumatic stress disorder. A clue to aetiology and treatment. Br J Psychiatry 1998;173:102–4.
[12] Prandoni P, Lensing AW, Prins MH, Ciammaichella M, Perlati M, Mumoli N, et al. Prevalence of pulmonary embolism among patients hospitalized for Syncope. N Engl J Med 2016;375:1524–31.
[13] Keller K, Beule J, Balzer JO, Dippold W. Syncope and collapse in acute pulmonary embolism. Am J Emerg Med 2016;34:1251–7.
[14] Soteriades ES, Evans JC, Larson MG, Chen MH, Chen L, Benjamin EJ, et al. Incidence and prognosis of syncope. N Engl J Med 2002;347:878–85.
[15] Internet page of the InEK GmbH – Institut für das Entgeltsystem im Krankenhaus vanO. Deutsche Kodierrichtlinien 2018 Druckversion A4 (PDF). https://wwwg-drgde/inek_site_de/layout/set/standard/Media/Files/G-DRG-System/G-DRG-System_2018/Deutsche_Kodierrichtlinien_2018_Druckversion_A4_PDF. 2018.
[16] Huff JS, Decker WW, Quinn JV, Perron AD, Napoli AM, Peeters S, et al. Clinical policy: critical issues in the evaluation and management of adult patients presenting to the emergency department with syncope. Ann Emerg Med 2007;49:431–44.
[17] Guldner S, Langada V, Popp S, Heppner HJ, Mang H, Christ M. Patients with syncope in a German emergency department: description of patients and processes. Dtsch Arztebl Int 2012;109:58–65.
[18] da Silva RM. Syncope: epidemiology, etiology, and prognosis. Front Physiol 2014;5:471.
[19] Alshekhlee A, Shen WK, Mackall J, Chelimsky TC. Incidence and mortality rates of syncope in the United States. Am J Med 2009;122:181–8.
[20] Brignole M, Gianfranchi L, Menozzi C, Raviele A, Oddone D, Lolli G, et al. Role of autonomic reflexes in syncope associated with paroxysmal atrial fibrillation. J Am Coll Cardiol 1993;22:1123–9.
[21] Alboni P, Menozzi C, Brignole M, Paparella N, Lolli G, Oddone D, et al. An abnormal neural reflex plays a role in causing syncope in sinus bradycardia. J Am Coll Cardiol 1993;22:1130–4.
[22] Arthur W, Kaye GC. The pathophysiology of common causes of syncope. Postgrad Med J 2000;76:750–3.
[23] Arnar DO. Syncope in patients with structural heart disease. J Intern Med 2013;273:336–44.
[24] Koplan BA, Stevenson WG. Ventricular tachycardia and sudden cardiac death. Mayo Clin Proc 2009;84:289–97.
[25] de Bakker JM, van Capelle FJ, Janse MJ, Wilde AA, Coronel R, Becker AE, et al. Reentry as a cause of ventricular tachycardia in patients with chronic ischemic heart disease: electrophysiologic and anatomic correlation. Circulation 1988;77:589–606.
[26] Stevenson WG, Sweeney MO. Arrhythmias and sudden death in heart failure. Jpn Circ J 1997;61:727–40.
[27] Hussain S, Jerry CL. Syncope and atrial fibrillation: which is the chicken and which is the egg? J Atr Fibrillation 2015;8:1175.
[28] Kamel H, Okin PM, Elkind MS, Iadecola C. Atrial fibrillation and mechanisms of stroke: time for a new model. Stroke 2016;47:895–900.
[29] Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS: the task force for the management of atrial fibrillation of the European Society of Cardiology (ESC)developed with the special contribution of the European heart rhythm association (EHRA) of the ESC endorsed by the European stroke organisation (ESO). Eur Heart J 2016;2016.
[30] Fuller CJ, Reisman M. Stroke prevention in atrial fibrillation: atrial appendage closure. Curr Cardiol Rep 2011;13:159–66.
[31] Middlekauff HR, Stevenson WG, Stevenson LW, Saxon LA. Syncope in advanced heart failure: high risk of sudden death regardless of origin of syncope. J Am Coll Cardiol 1993;21:110–6.

[32] Kapoor WN, Karpf M, Wieand S, Peterson JR, Levey GS. A prospective evaluation and follow-up of patients with syncope. N Engl J Med 1983;309:197–204.
[33] Wasek W, Kulakowski P, Czepiel A, Klosiewicz-Wasek B, Budaj A, Soszynska M, et al. Susceptibility to neuromediated syncope after acute myocardial infarction. Eur J Clin Invest 2000;30:383–8.
[34] Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey Jr. DE, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (writing committee to revise the 2002 guidelines for the Management of Patients with Unstable Angina/non-ST-elevation myocardial infarction) developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. J Am Coll Cardiol 2007;50:e1–157.
[35] Demircan A, Aygencel G, Keles A, Ozsoylar O, Bildik F. Pulmonary embolism presenting as syncope: a case report. J Med Case Rep 2009;3:7440.
[36] Simpson Jr. RJ, Podolak R, Mangano Jr. CA, Foster JR, Dalldorf FG. Vagal syncope during recurrent pulmonary embolism. JAMA 1983;249:390–3.
[37] Morpurgo M, Zonzin P. Syncope in acute pulmonary embolism. Ital Heart J 2004;5:3–5.
[38] Akinboboye OO, Brown Jr. EJ, Queirroz R, Cusi VP, Horowitz LF, Jonas EA, et al. Recurrent pulmonary embolism with second-degree atrioventricular block and near syncope. Am Heart J 1993;126:731–2.
[39] Mark AL. The Bezold-Jarisch reflex revisited: clinical implications of inhibitory reflexes originating in the heart. J Am Coll Cardiol 1983;1:90–102.
[40] Castelli R, Tarsia P, Tantardini C, Pantaleo G, Guariglia A, Porro F. Syncope in patients with pulmonary embolism: comparison between patients with syncope as the presenting symptom of pulmonary embolism and patients with pulmonary embolism without syncope. Vasc Med 2003;8:257–61.
[41] Simonis G, Gerk U, Pabst F, Machetanz J, Spitzer SG, Schellong S. Reflex syncope and syncope secondary to orthostatic hypotension. Internist (Berl) 2015;56:12–9.
[42] Gerk U, Simonis G, Machetanz J, Pabst F, Schellong S. Cardiogenic syncope. Internist (Berl) 2015;56:20–8.
[43] Sorensen HT, Horvath-Puho E, Lash TL, Christiansen CF, Pesavento R, Pedersen L, et al. Heart disease may be a risk factor for pulmonary embolism without peripheral deep venous thrombosis. Circulation 2011;124:1435–41.
[44] Keller K, Prochaska JH, Coldewey M, Gobel S, Ullmann A, Junger C, et al. History of deep vein thrombosis is a discriminator for concomitant atrial fibrillation in pulmonary embolism. Thromb Res 2015;136:899–906.
[45] Lee Y-H, Cha S-I, Shin K-M, Lim J-K, Yoo S-S, Lee S-Y, et al. Clinical relevance of syncope in patients with pulmonary embolism. Thromb Res 2018;164:85–9.
[46] Konstantinides S, Torbicki A, Agnelli G, Danchin N, Fitzmaurice D, Galie N, et al. ESC guidelines on the diagnosis and management of acute pulmonary embolism: the task force for the diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC)endorsed by the European Respiratory Society (ERS). Eur Heart J 2014:2014.
[47] Meyer G, Vicaut E, Danays T, Agnelli G, Becattini C, Beyer-Westendorf J, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med 2014;370:1402–11.
[48] Chen JH, Chang SS, Liu JJ, Chan RC, Wu JY, Wang WC, et al. Comparison of clinical characteristics and performance of pneumonia severity score and CURB-65 among younger adults, elderly and very old subjects. Thorax 2010;65:971–7.
[49] Bauer TT, Ewig S, Marre R, Suttorp N, Welte T. CRB-65 predicts death from community-acquired pneumonia. J Intern Med 2006;260:93–101.