IJC Heart & Vasculature 53 (2024) 101470

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: www.sciencedirect.com/journal/ijc-heart-and-vasculature

Sarcopenia influences usage of reperfusion treatment in patients with pulmonary embolism aged 75 years and older

Karsten Keller [a,b,c,*], Volker H. Schmitt [a,d], Christoph Brochhausen [e], Omar Hahad [a,d], Martin Engelhardt [f,g], Christine Espinola-Klein [a,b], Thomas Münzel [a,d], Philipp Lurz [a,d], Stavros Konstantinides [b,h], Lukas Hobohm [a,b]

[a] Department of Cardiology, University Medical Center of the Johannes Gutenberg-University Mainz, Mainz, Germany
[b] Center for Thrombosis and Hemostasis (CTH), University Medical Center of the Johannes Gutenberg-University Mainz, Mainz, Germany
[c] Medical Clinic VII, Department of Sports Medicine, University Hospital Heidelberg, Heidelberg, Germany
[d] German Center for Cardiovascular Research (DZHK), Partner Site Rhine-Main, Mainz, Germany
[e] Institute of Pathology, University Medical Center Mannheim, Heidelberg University, Germany
[f] Department for Orthopedics, Trauma surgery and Hand surgery, Klinikum Osnabrück, Osnabrück, Germany
[g] Institute for Applied Training Science Leipzig, Germany
[h] Department of Cardiology, Democritus University of Thrace, Alexandroupolis, Greece

ARTICLE INFO

Keywords:
Pulmonary embolism
Sarcopenia
Clinical outcome
Epidemiology
Frailty
Skeletal muscle impairment
Geriatric patients

ABSTRACT

Background: Although pulmonary embolism (PE) and sarcopenia are common diseases, only a few studies have assessed the impact of sarcopenia in PE on usage of reperfusion treatments in PE.
Methods: All hospitalizations of PE patients aged ≥75 years 2005–2020 in Germany were included in this study and stratified for sarcopenia. Impact of sarcopenia on treatment procedures and adverse in-hospital events were investigated.
Results: Overall, 576,364 hospitalizations of PE patients aged ≥75 years (median age 81.0 [78.0–85.0] years; 63.3 % females) were diagnosed in Germany during the observational period 2005–2020. Among these, 2357 (0.4 %) were coded with sarcopenia. PE patients with sarcopenia were in median 2 years older (83.0 [79.0–87.0] vs. 81.0 [78.0–85.0] years, P<0.001) and showed an aggravated comorbidity-profile (Charlson Comorbidity Index 7.00 [5.00–9.00] vs. 6.00 [4.00–7.00], P<0.001). Although signs of hemodynamic compromise such as shock (5.2 % vs. 4.1 %, P=0.005) and tachycardia (4.1 % vs. 2.8 %, P<0.001) were more prevalent in sarcopenic PE patients, systemic thrombolysis (1.9 % vs. 3.5 %, P<0.001) was less often used in these patients. Sarcopenia was independently related to an underuse of systemic thrombolysis (OR 0.537 [95 %CI 0.398–0.725], P<0.001). This underuse might driven by higher rates of bleeding events (gastro-intestinal bleeding: 3.1 % vs. 1.9 %, P<0.001, necessity of transfusion of blood constituents: 18.9 % vs. 11.3 %, P<0.001), but also stroke (5.6 % vs. 3.3 %, P<0.001).
Conclusions: Sarcopenia represents a widely overlooked condition in PE patients. Although sarcopenic PE patients were more often afflicted by hemodynamic compromise, systemic thrombolysis was less often administered. This underuse might be caused by contraindications like bleeding events and stroke.

1. Introduction

Pulmonary embolism (PE) is an important cause of morbidity and mortality worldwide.[1–3] PE occurs when venous thrombi embolize to the pulmonary circulation resulting vascular occlusion with impaired circulation and gas exchange [2–4]. Initial risk stratification of PE is based on clinical symptoms, cardiac adaptations, signs of haemodynamic compromise and especially instability and also on age as well as comorbidities [2,3]. The primary aim of the treatment for PE is to restore blood flow to the affected areas of the lungs, resolve/remove embolus, reduce cardiac overload, and prevent further clot formation [2,3]. Since acute right ventricular failure (with the result of a low systemic output) is the leading cause of death in patients with high-risk PE (haemodynamic instability according to the ESC algorithm) and also

* Corresponding author at: Center Mainz, Johannes Gutenberg-University Mainz, Langenbeckstrasse 1, 55131 Mainz Germany.
E-mail address: Karsten.Keller@unimedizin-mainz.de (K. Keller).

https://doi.org/10.1016/j.ijcha.2024.101470
Received 21 May 2024; Received in revised form 12 July 2024; Accepted 15 July 2024

in selected patients with threatening hemodynamic compromise (intermediate high-risk), immediate reperfusion is recommended in this crucial patient group [2]. Systemic thrombolysis as well as surgical embolectomy are established treatment options and catheter-directed therapies is a new emergent approach to encounter hemodynamic compromise in PE [2]. The usage of these treatments, but especially the usage of thrombolysis, is influenced and hampered by contraindications, but also by physicians' and patients' fear for bleeding events, physicians' knowledge as well as the implementation of PE response teams (PERT) in the hospitals.[3,5–7] In this context, it is of outstanding importance that the incidence of PE increases substantially with age.[3,8] With the aging of the Western populations and the demographic change, incidence of PE will rise and will increase the health burden on the different health care systems in combination and/or in interaction with other comorbidities and conditions triggered by older age.[9,10]

Besides increasing prevalence of PE and atherosclerotic diseases with advanced age [11–13], also other conditions like sarcopenia are more common in the aging population.[14–16] Sarcopenia is a frequently overlooked disease and consecutively, an undertreated syndrome comprising pronounced muscle mass as well as strength/performance loss. [14,17–19] The estimated prevalence of sarcopenia in the general population ranges between 5 and 40 % and is accompanied by an exponential increase with increasing age.[14,18,20] Hormonal changes, nutritional deficiencies, chronic inflammation, and decreased physical activity are the main causes of sarcopenia.[14,21] Although PE as well as sarcopenia are common diseases, only a few studies have assessed the impact of sarcopenia in PE and data regarding the impact of sarcopenia on the usage of reperfusion treatments in patients with PE are missing. [22,23] Therefore, the aim of the present study was to close this gap of knowledge.

2. Methods

2.1. Data source

We analysed all hospitalization cases of patients aged ≥75 years with PE in Germany during the timeframe of the years 2005–2020 (source: RDC of the Federal Statistical Office and the Statistical Offices of the federal states, DRG Statistics 2005–2020, and own calculations). Thus, for this present study, we included all hospitalized patient-cases of patients aged ≥75 years with a diagnosis of PE (ICD-code I26) [3,24].

In Germany, patients' diagnoses have to be coded according to the established coding guidelines ICD-10-GM (International Classification of Diseases, 10th Revision with German Modification) and diagnostical, surgical as well as interventional procedures have to be assessed with OPS codes (surgery, diagnostic and procedures codes [Operationen- und Prozedurenschlüssel]) for reimbursement reasons.[3,25] In addition, the Federal Statistical Office of Germany (Statistisches Bundesamt, Wiesbaden, Germany) gathers all data from all inpatient cases in Germany, which are coded and processed according to the diagnosis related groups [DRG] system for research purposes.

In this context, the statistical analyses of this present study were computed on our behalf by the Research Data Center (RDC) of the Federal Bureau of Statistics (Wiesbaden, Germany). The RDC provides aggregated statistics of the gathered data for research purpose on the basis of our previously generated and sent SPSS codes (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. IBM Corp: Armonk, NY, USA).

As aforementioned, we included all hospitalizations of patients with PE (identified by main or secondary diagnosis: ICD-code I26) during the observational period in Germany in this study. Among the hospitalization-cases of PE patients, these patients were stratified for the presence of sarcopenia (ICD-code M62.5). We compared PE patients with and without sarcopenia and analysed the impact of sarcopenia on cardiovascular profile as well as reperfusion treatments and adverse in-hospital events. Additionally, temporal trends in these patients regarding total numbers, adverse in-hospital events and mentioned treatments were investigated.

2.2. Study outcomes and adverse in-hospital events

The primary study outcome was defined as the usage of the reperfusion treatments systemic thrombolysis, surgical embolectomy and catheter-directed therapies. The secondary outcome comprises the prevalence of bleeding events such as intracerebral bleeding events (ICB, ICD-code I61), gastro-intestinal bleeding (GIB, ICD-codes K920-K922), and bleeding events with necessity of transfusion of blood components (OPS code 8–800). Furthermore, prolonged in-hospital stay (>10 days) as well as additional adverse events during in-hospital stay such as pneumonia (ICD-codes J12-J18), acute kidney injury (AKI, ICD-code N17) and stroke (ischemic and hemorrhagic stroke, ICD-codes I61-64) were assessed.

2.3. Definitions of covariates and outcomes

Obesity was defined according to the recommendations of the WHO (World Health Organization) as a body mass index ≥30 kg/m^2 [26]. Severe PE was defined as presence of tachycardia (ICD-10 codes I47 and R00.0), RV dysfunction (I26.0), shock (R57) and/or cardio-pulmonary resuscitation (OPS code 8–77). Shock as well as cardio-pulmonary resuscitation were defined according to current European guidelines [7,27–29]. As aforementioned, prolonged in-hospital stay was defined as a long in-hospital stay longer than 10 days.

2.4. Ethical aspects

In accordance with the German law, an approval by an ethical committee as well as informed consent of the patients were both not required, since the present study did not involve a direct access of us as the study investigators to individual patient-level data, but only on summarized/aggregated data provided by the RDC.

2.5. Statistical methods

Descriptive statistical comparisons of hospitalizations of PE patients aged ≥75 years with and without sarcopenia were calculated as median and interquartile range (IQR) or as absolute numbers and corresponding percentages. Continuous variables were compared by the help of the Mann-Whitney-*U* test and for the comparisons of categorical variables the Fisher's exact or the chi^2 test were used, as appropriate.

Temporal trends of hospitalizations of PE patients and PE patients with sarcopenia as well as usage of performed reperfusion were calculated on an annual and age-dependent (age-decade) basis. Linear regressions were used to assess trends over time and the results are shown as beta (β) with corresponding 95 % confidence intervals (CI).

The investigation of the impact of sarcopenia on usage of reperfusion treatments, prolonged in-hospital stay, bleeding events and other adverse in-hospital events in PE patients, which might be treatment complications, was performed with the use of univariable and multivariable logistic regression models. Results are given as odds ratio (OR) and 95 % CI. The multivariable regression models were adjusted for age, sex, obesity, hyperlipidemia, cancer, coronary artery disease, heart failure, chronic obstructive pulmonary disease, essential arterial hypertension, acute and/or chronic kidney failure, diabetes mellitus and atrial fibrillation/flutter. Notably, we selected this epidemiological approach for the adjustment with age, sex and all mentioned comorbidities to test the widespread independence of the results regarding sarcopenia as an independent predictor on the different outcomes/endpoints.

Statistical significance was given in cases of a P-value <0.05 (two-sided). Statistical analyses were performed with the software SPSS®

(version 20.0; SPSS Inc., Chicago, Illinois, USA).

3. Results

Overall, 576,364 hospitalizations of PE patients aged ≥75 years (median age 81.0 [78.0–85.0] years; 63.3 % females) were diagnosed in Germany during the observational period 2005–2020. The median length of in-hospital stay was 10.0 (IQR 6.0–17.0) days. In-hospital mortality of all hospitalized PE patients aged ≥ 75 years was 20.3 %.

Table 1
Patients' characteristics, medical history, presentation and adverse in-hospital events of the 576,364 hospitalizations of patients with PE aged ≥75 years in Germany in the years 2005–2020 stratified for presence of sarcopenia.

Parameters	PE patients without sarcopenia (n = 574,007; 99.6 %)	PE patients with sarcopenia (n = 2357; 0.4 %)	P-value
Age	81.00 (78.00–85.00)	83.00 (79.00–87.00)	**<0.001**
Female sex	363,464 (63.3 %)	1579 (67.0 %)	**<0.001**
In-hospital stay (days)	10.00 (6.00–17.00)	20.00 (14.00–28.00)	**<0.001**
In-hospital stay >10 days	274,443 (47.8 %)	1943 (82.4 %)	**<0.001**
Cardiovascular risk factors			
Obesity	36,706 (6.4 %)	214 (9.1 %)	**<0.001**
Essential arterial hypertension	299,515 (52.2 %)	1275 (54.1 %)	0.063
Diabetes mellitus	131,329 (22.9 %)	609 (25.8 %)	**0.001**
Hyperlipidaemia	86,782 (15.1 %)	389 (1.5 %)	0.061
VTE risk factors			
Cancer	91,391 (15.9 %)	405 (17.2 %)	0.095
Any surgery	286,677 (49.9 %)	1992 (84.5 %)	**<0.001**
Thrombophilia	2379 (0.4 %)	9 (0.4 %)	1.000
Comorbidities			
Heart failure	178,083 (31.0 %)	1041 (44.2 %)	**<0.001**
Coronary artery disease	109,916 (19.1 %)	486 (20.6 %)	0.070
Peripheral artery disease	20,836 (3.6 %)	126 (5.3 %)	**<0.001**
Atrial fibrillation/flutter	134,772 (23.5 %)	732 (31.1 %)	**<0.001**
Chronic obstructive pulmonary disease	65,326 (11.4 %)	295 (12.5 %)	0.083
Acute or chronic kidney failure	181,258 (31.6 %)	1088 (46.2 %)	**<0.001**
Chronic anaemia	51,770 (9.0 %)	423 (17.9 %)	**<0.001**
Charlson comorbidity index	6.00 (4.00–7.00)	7.00 (5.00–9.00)	**<0.001**
Treatment escalation and reperfusion treatments			
Systemic thrombolysis	19,886 (3.5 %)	44 (1.9 %)	**<0.001**
Intensive care unit	89,786 (15.6 %)	440 (18.7 %)	**<0.001**
Risk stratification markers and deep venous thrombosis/thrombophlebitis			
Deep venous thrombosis/ thrombophlebitis	185,482 (32.3 %)	608 (25.8 %)	**<0.001**
Tachycardia	15,911 (2.8 %)	97 (4.1 %)	**<0.001**
Syncope	18,765 (3.3 %)	78 (3.3 %)	0.913
RV dysfunction	177,560 (30.9 %)	629 (26.7 %)	**<0.001**
Shock	23,389 (4.1 %)	123 (5.2 %)	**0.005**
Adverse events during hospitalization			
Acute kidney failure	45,370 (7.9 %)	320 (13.6 %)	**<0.001**
Pneumonia	132,839 (23.1 %)	732 (31.1 %)	**<0.001**
Stroke (ischaemic or haemorrhagic)	18,742 (3.3 %)	131 (5.6 %)	**<0.001**
Intracerebral bleeding	3013 (0.5 %)	18 (0.8 %)	0.110
Gastro-intestinal bleeding	10,675 (1.9 %)	73 (3.1 %)	**<0.001**
Transfusion of blood constituents	64,680 (11.3 %)	446 (18.9 %)	**<0.001**

Among the hospitalizations, 2357 (0.4 %) were coded with sarcopenia (Table 1).

Notably, annual total numbers of sarcopenic PE patients increased from 19 (0.07 %) in the year 2005 to 342 (0.84 %) in 2020 (β 2.818 [95 %CI 2.635 to 3.000], P<0.001) (Fig. 1).

3.1. Patient characteristics

PE patients with sarcopenia were in median 2 years older (83.0 [79.0–87.0] vs. 81.0 [78.0–85.0] years, P<0.001), more often female (67.0 % vs. 63.3 %, P<0.001), obese (9.1 % vs. 6.4 %, P<0.001) and had more often comorbidities such as diabetes mellitus (25.8 % vs. 22.9 %, P<0.001), heart failure (44.2 % vs. 31.0 %, P<0.001), peripheral artery disease (5.3 % vs. 3.6 %, P<0.001), atrial fibrillation/flutter (31.1 % vs. 23.5 %, P<0.001), acute or chronic kidney failure (46.2 % vs. 31.6 %, P<0.001) and chronic anaemia (17.9 % vs. 9.0 %, P<0.001), mirrored in a higher Charlson Comorbidity Index (CCI) Score of PE patients with sarcopenia (7.00 [5.00–9.00] vs. 6.00 [4.00–7.00] points, P<0.001) (Table 1). Regarding classical risk factors for venous thromboembolism (VTE), prevalence of cancer (P=0.095) and thrombophilia (P=1.000) was similar in both groups, while surgery as strong VTE risk factor was more frequently seen in sarcopenic PE patients (84.5 % vs. 49.9 %, P<0.001) (Table 1). Sarcopenia was associated with increased CCI identifying an aggravated comorbidity burden in PE patients with sarcopenia (OR 1.185 [95 %CI 1.168–1.203], P<0.001).

3.2. Signs of hemodynamic compromise and reperfusion treatments

Since signs of hemodynamic compromise such as shock (5.2 % vs. 4.1 %, P=0.005) and tachycardia (4.1 % vs. 2.8 %, P<0.001) are more prevalent in PE patients with sarcopenia, sarcopenic PE patients were more often admitted to an ICU (18.7 % vs. 15.6 %, P<0.001) (Table 1). In contrast, RV dysfunction (26.7 % vs. 30.9 %, P<0.001) was less often detected in PE patients with sarcopenia. Summarizing these results, severe PE was detected in 700 (31.5 %) of the sarcopenic PE patients. However, the reperfusion treatment of systemic thrombolysis (1.9 % vs. 3.5 %, P<0.001) was less often used in sarcopenic PE patients compared to those without sarcopenia. In contrast, the usage of catheter-directed treatment (P=0.276) as well as surgical embolectomy (P=0.440) does not differ significantly between both patient groups.

The logistic regression analysis adjusted for age, sex and comorbidities showed that sarcopenia was related to an underuse of systemic thrombolysis (OR 0.537 [95 %CI 0.398–0.725], P<0.001) especially in the light of higher rate of hemodynamic compromise as aforementioned (Table 2), while the use of catheter-directed treatment (P=0.242) and surgical embolectomy (P=0.552) were not affected. This difference between the proportion of sarcopenic patients with severe PE and the rate regarding administration of systemic thrombolysis (as the standard of care) characterize the underuse of systemic thrombolysis. This difference/underuse was seen for all investigated 5-year age-categories (Fig. 2): This discrepancy between the proportions of sarcopenic patients with severe PE and of the usage of systemic thrombolysis was in the age group 75–79 years 32.2 %, in the age-group 80–84 years 29.0 %, in the age-group 85–89 years 28.9 % and in the patients aged 90 years and older 28.9 %.

3.3. Length of in-hospital stay

Length of in-hospital stay was longer in PE patients with sarcopenia than without (20.00 [14.00–28.00] vs. 10.00 [6.00–17.00] days, P<0.001). Consecutively, a prolonged in-hospital stay longer than 10 days (82.4 % vs. 47.8 %, P<0.001) was also more commonly identified in PE patients with sarcopenia (Table 1). Sarcopenia in PE patients was independently associated with a prolonged length of in-hospital stay of > 10 days (OR 4.826 [95 %CI 4.314–5.398], P<0.001) (Table 2).

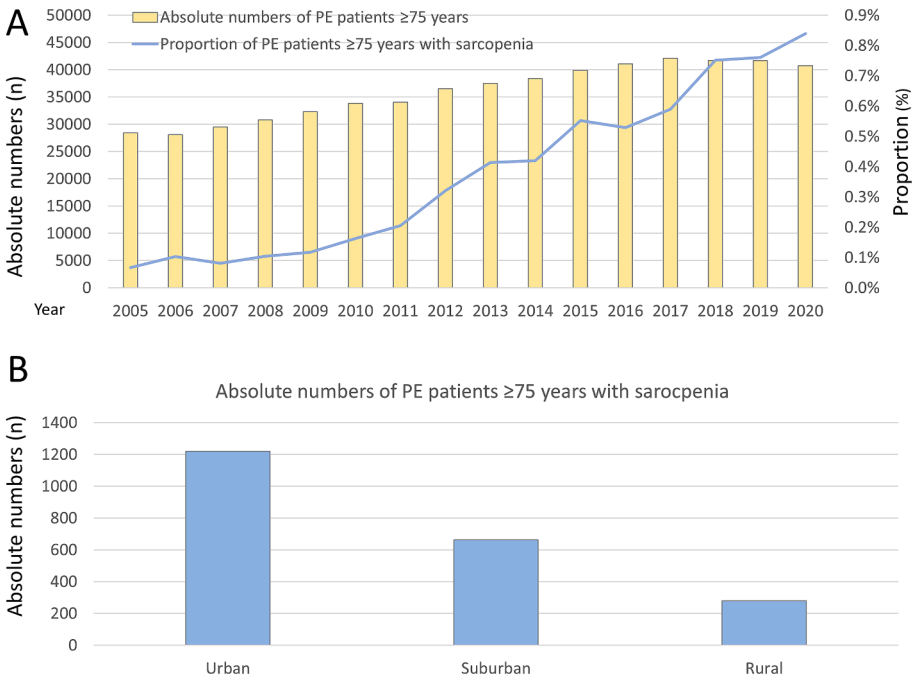

Fig. 1. Temporal and regional trends regarding hospitalizations of patients with PE and proportion of additional sarcopenia. Panel A – Total annual numbers regarding hospitalizations of PE patients with sarcopenia and proportion of PE patients with sarcopenia related to all annual hospitalizations with PE stratified during the observational period 2005–2020. **Panel B** — Regional trends regarding hospitalizations of PE patients with sarcopenia.

3.4. Bleeding events

The investigated bleeding events including gastro-intestinal bleeding (3.1 % vs. 1.9 %, P<0.001) and necessity of transfusion of blood constituents (18.9 % vs. 11.3 %, P<0.001) occurred more often in PE patients with sarcopenia compared to those without, whereby intracerebral bleeding (0.8 % vs. 0.5 %, P=0.110) was similarly often present in both groups (Table 1). Sarcopenia was independently associated with all investigated bleeding events including intracerebral bleeding (OR 1.611 [95 %CI 1.011–2.568], P=0.045), gastro-intestinal bleeding (OR 1.486 [95 %CI 1.175–1.878], P=0.001) and necessity regarding transfusion of blood constituents (OR 1.624 [95 %CI 1.455–1.812], P<0.001) (Table 2).

When focusing on the 184,210 PE hospitalizations of PE patients with severe PE, sarcopenia was independently associated with an increased need for transfusion of blood constituents (OR 1.765 [95 %CI 1.481–2.105], P<0.001). Among these, 700 sarcopenic PE patients with severe PE were coded (31.5 % of the PE patients with sarcopenia). In this crucial patient group, systemic thrombolysis was not independently afflicted by increased occurrence of bleeding with a need for transfusion of blood constituents (OR 1.150 [95 %CI 0.464–2.850], P=0.763).

3.5. Further investigated adverse in-hospital events

Pneumonia (31.1 % vs. 23.1 %, P<0.001), stroke (5.6 % vs. 3.3 %, P<0.001) and acute kidney failure (13.6 % vs. 7.9 %, P<0.001) were more prevalent in patients with sarcopenia in comparison to those without (Table 1). The logistic regression analyses also showed an independent association between sarcopenia with increased risk for pneumonia (OR 1.402 [95 %CI 1.283–1.532], P<0.001), stroke (OR 1.734 [95 %CI 1.451–2.072], P<0.001) and acute renal failure (OR 1.245 [95 %CI 1.091–1.421], P=0.001) (Table 2).

4. Discussion

Sarcopenia is a geriatric condition characterized by a progressive loss of muscle mass and function, which is associated with various adverse health outcomes.[14,19,30,31] The prevalence of sarcopenia varies widely between the investigating studies and especially depending on the used definition of sarcopenia. [14,30,31] It was estimated, that sarcopenia impacts approximately between 5 and 17 % of the aging population worldwide. [30,32] Notably, the prevalence of sarcopenia among patients with chronic diseases was higher than in the general population.[30] For example, the reported prevalence of sarcopenia in patients with diabetes mellitus was with 18 % and the prevalence of sarcopenia in patients with unresectable esophageal cancer was with 66 % substantially higher than the reported prevalence of sarcopenia in the general population.[30] Sarcopenia (as a skeletal muscle disorder) was in studies associated with increased likelihood of adverse outcomes including falls, fractures, physical disability, but also mortality. [14,30–39] Although we did not expect a high prevalence of sarcopenia in our study investigating patients with an acute PE as an emergency case, the rate of sarcopenia in these PE patients was very low in comparison to the reported prevalence of sarcopenia in the aforementioned chronic diseases.[1–3,30] In this context, the prevalence of 0.4 % PE patients who were coded with sarcopenia is considerably lower than expected and indicates for a low awareness regarding sarcopenia of German health care physicians during emergency situations.[40] Our study results indicate for a small increase regarding the awareness of sarcopenia during the observational period 2005–2020 elucidated in the increasing numbers of coded PE cases with sarcopenia. This finding is in accordance with the literature demonstrating that healthcare professionals had low awareness as well as limited knowledge of sarcopenia, which might influence and hinder the diagnosis and treatment of sarcopenia in health care practice.[41,42] While the median length of in-hospital stay was 10 days in the PE patients aged ≥75 years, sarcopenia was significantly and independently associated with a longer length of in-hospital stay >10 days, which is in line with the literature. [43].

Besides these expected results, the main focus of this study was to detect the impact of sarcopenia on the usage of reperfusion treatments in patients with PE since data in this field are widely missing. [22,23].

It is important that our study results demonstrated an aggravated comorbid burden in PE patients with sarcopenia, which is in accordance

Table 2
Impact of sarcopenia on adverse events during in-hospital stay in patients aged ≥75 years with PE (univariate and multivariate logistic regression model).

	Univariate regression model		Multivariate regression model*	
	OR (95 % CI)	P-value	OR (95 % CI)	P-value
Adverse events during in-hospital stay				
In-hospital stay >10 days	5.167 (4.626–5.771)	**<0.001**	4.826 (4.314–5.398)	**<0.001**
Pneumonia	1.496 (1.371–1.633)	**<0.001**	1.402 (1.283–1.532)	**<0.001**
Tachycardia	1.505 (1.228–1.846)	**<0.001**	1.359 (1.108–1.668)	**0.003**
Syncope	1.013 (0.808–1.270)	0.913	0.985 (0.785–1.235)	0.894
RV dysfunction	0.813 (0.742–0.891)	**<0.001**	0.736 (0.671–0.808)	**<0.001**
Shock	1.284 (1.062–1.553)	**0.010**	1.624 (1.455–1.812)	**<0.001**
Acute renal failure	1.830 (1.626–2.060)	**<0.001**	1.245 (1.091–1.421)	**0.001**
Stroke (ischaemic or haemorrhagic)	1.744 (1.461–2.081)	**<0.001**	1.734 (1.451–2.072)	**<0.001**
Intracerebral bleeding	1.458 (0.916–2.322)	0.112	1.611 (1.011–2.568)	**0.045**
Gastro-intestinal bleeding	1.687 (1.335–2.131)	**<0.001**	1.486 (1.175–1.878)	**0.001**
Transfusion of blood constituents	2.123 (1.784–2.528)	**<0.001**	1.624 (1.455–1.812)	**<0.001**
Treatments				
Systemic thrombolysis	0.530 (0.393–0.715)	**<0.001**	0.537 (0.398–0.725)	**<0.001**
Catheter-directed treatment	0.287 (0.040–2.041)	0.212	0.310 (0.044–2.207)	0.242
Surgical embolectomy	1.592 (0.396–6.399)	0.512	1.526 (0.379–6.143)	0.552
Intensive care unit	1.233 (1.107–1.373)	**<0.001**	1.135 (1.021–1.262)	**0.019**

* Adjustment: Adjusted for age, sex, obesity, hyperlipidemia, cancer, coronary artery disease, heart failure, chronic obstructive pulmonary disease, essential arterial hypertension, acute and/or chronic kidney failure, diabetes mellitus and atrial fibrillation/flutter.

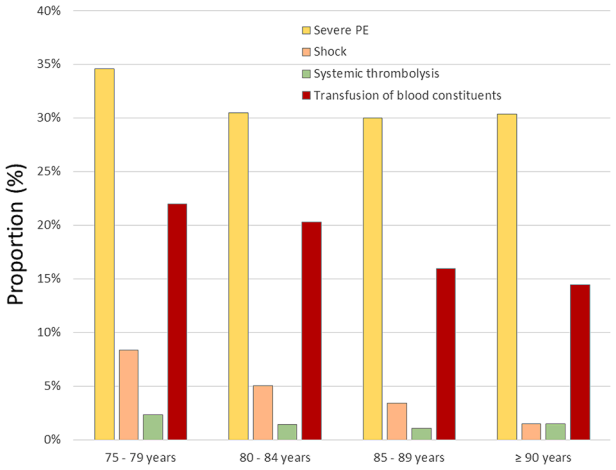

Fig. 2. Age-dependent trends regarding severe PE, shock, systemic thrombolysis and transfusion of blood constituents in sarcopenic PE patients stratified for 5-year age-categories.

with previously published studies.[44] In addition, the signs of hemodynamic compromise such as shock were more prevalent in PE patients with sarcopenia. According these markers of initial risk stratification of PE primarily based on signs of haemodynamic compromise/instability, cardiac adaptations as well as comorbid burden [2,3], sarcopenic PE patients have to be categorized more often as high-risk PE (haemodynamic instability according to the ESC algorithm). In those patients with high-risk PE, but also in selected patients with threatening hemodynamic compromise (intermediate high-risk), an immediate reperfusion is recommended by the European and American guidelines. [2,45] Thus, according to guideline recommendations, a higher rate of reperfusion strategies has to be expected in sarcopenic PE patients.[2,3,45] In contrast to this expectation, we detected a lower reperfusion rate and therefore an underuse of reperfusion treatments in this crucial patient group. In particular, the standard approach of reperfusion treatment—systemic thrombolysis—was used less than half as often in PE patients with sarcopenia in comparison to non-sarcopenic patients. However, the usage of catheter-directed treatment as well as surgical embolectomy did not differ significantly between both patient groups, but the total numbers of these additionally reperfusion treatments were very low. Systemic thrombolysis is a well-established treatment strategy to oppose hemodynamic compromise in PE to save the life of patients with acute right heart failure and shock/hemodynamic instability. [2] Nevertheless, in accordance with our present study, various studies detected an underuse of these treatment options in PE patients with hemodynamic compromise. [3,46,47] In our present study, it has to be suggested that the decision regarding usage of systemic thrombolysis was influenced by contra-indications such as bleeding events, but also renal impairment and stroke, which were in our present investigation all more prevalent in sarcopenic PE patients. The results of our study revealed an underuse of systemic thrombolysis in all investigated age-groups of sarcopenic PE patients aged 75 years and older. In this context, our results demonstrated that sarcopenia is afflicted by increased bleeding risk in PE patients. These findings are in accordance with literature. [3,46,47] Nevertheless, physicians' and patients' fear for bleeding events as the most decisive and crucial factors to decide against the recommended reperfusion strategies might be more pronounced in presence of sarcopenia. Consequently, these contraindications might at least in part the reason for lower rates regarding the administration of systemic thrombolysis in sarcopenic PE patients. The implementation of PERTs in hospitals might help to overcome uncertainty and solve the problem of hesitant decision making in some of these patients in the future.[3,5–7,48] In addition, the awareness regarding sarcopenia has to be broadened to identify affected patients and focus on the additional needs of this crucial patient group.[41,42] Since sarcopenia was found to be associated with both decreased cognitive and mobility domains, a tailored and multi-dimensional training intervention and rehabilitation should be pursued after the acute course of PE aiming to improve patients' functional recovery and increase quality of life.[49–51].

5. Conclusions

Sarcopenia represents a widely overlooked and underestimated condition in patients with PE. However, the awareness increases on a low level. Although sarcopenic PE patients are more often afflicted by hemodynamic compromise and aggravated comorbidity profile, in those sarcopenic patients with high-risk or intermediate high-risk PE the recommended and life-saving reperfusion treatments are not administered. This underuse might be caused in part by the presence of contraindications like bleeding events and stroke.

6. Limitations

In the present study some key limitations should be considered: Due to the nature of an ICD- and OPS-code-based study-analysis for hospitalized patients, under-reporting and under-coding might be possible and may be a biasing factor. The low detected prevalence of sarcopenia in our study indicates for a low awareness regarding sarcopenia of the

health care physicians and related to that, an under-coding of sarcopenia in the PE cases can be assumed.[30,32,41] Thus, we could not be aware that the low awareness regarding sarcopenia might influence our results. However, since undetected and therefore not-coded sarcopenia cases should be also associated with aggravated patient-profile and an underuse of reperfusion treatments, the negative effect of sarcopenia on the use of reperfusion treatments in PE should even be mitigated, disguised and reduced. In addition, data on concomitant medication—especially on anticoagulant treatment—or laboratory markers are not available in the German nationwide inpatient sample. Furthermore, no follow-up data evaluation is possible since data for post-hospitalization period are not assessed and therefore limited to the time-frame of the in-hospital course.

Author contributions

KK and LH were responsible for the conception of the study and for acquisition as well as analysis of the data. All authors were responsible for interpretation of the data. KK drafted the article and all other authors revised it critically for important intellectual content.

Funding

None.

CRediT authorship contribution statement

Karsten Keller: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Volker H. Schmitt:** Writing – review & editing. **Christoph Brochhausen:** Writing – review & editing. **Omar Hahad:** Writing – review & editing. **Martin Engelhardt:** Writing – review & editing. **Christine Espinola-Klein:** Writing – review & editing. **Thomas Münzel:** Writing – review & editing. **Philipp Lurz:** Writing – review & editing. **Stavros Konstantinides:** Writing – review & editing. **Lukas Hobohm:** Writing – review & editing, Project administration, Investigation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [KK, VHS, CB, OH, ME and TM report no conflict of interests. CEK reports having from Amarin Germany, Amgen GmbH, Bayer Vital, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Leo Pharma, MSD Sharp & Dohme, Novartis Pharma, Pfizer Pharma GmbH, Sanofi-Aventis GmbH. PL has received institutional fees and research grants from Abbott Vascular, Edwards Lifesciences, and ReCor, honoraria from Edwards Lifesciences, Abbott Medical, Innoventric, ReCor and Boehringer Ingelheim and has stock options with Innoventric. SK reports institutional grants and personal lecture/advisory fees from Bayer AG, Daiichi Sankyo, and Boston Scientific; institutional grants from Inari Medical; and personal lecture/advisory fees from MSD and Bristol Myers Squibb/Pfizer. LH received lecture/consultant fees from Johnson&Johson, MSD, Boston Scientific and Inari Medical, outside the submitted work].

Acknowledgments

We thank the Federal Statistical Office of Germany (Statistisches Bundesamt, DEStatis) for providing the data/results and the kind permission to publish these results (source: RDC of the Federal Statistical Office and the Statistical Offices of the federal states, DRG Statistics 2005-2020, own calculations).

References

[1] S.V. Konstantinides, S. Barco, M. Lankeit, G. Meyer, Management of pulmonary embolism: an update, J. Am. Coll. Cardiol. 67 (2016) 976–990, https://doi.org/10.1016/j.jacc.2015.11.061.
[2] S.V. Konstantinides, G. Meyer, C. Becattini, H. Bueno, G.J. Geersing, V.P. Harjola, M.V. Huisman, M. Humbert, C.S. Jennings, D. Jimenez, et al., ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European respiratory society (ERS): the task force for the diagnosis and management of acute pulmonary embolism of the european society of cardiology (ESC), Eur. Respir. J. 2019 (2019) 54, https://doi.org/10.1183/13993003.01647-2019.
[3] K. Keller, L. Hobohm, M. Ebner, K.P. Kresoja, T. Munzel, S.V. Konstantinides, M. Lankeit, Trends in thrombolytic treatment and outcomes of acute pulmonary embolism in Germany, Eur. Heart J. 41 (2020) 522–529, https://doi.org/10.1093/eurheartj/ehz236.
[4] K. Keller, J. Beule, M. Coldewey, M. Geyer, J.O. Balzer, W. Dippold, The risk factor age in normotensive patients with pulmonary embolism: Effectiveness of age in predicting submassive pulmonary embolism, cardiac injury, right ventricular dysfunction and elevated systolic pulmonary artery pressure in normotensive pulmonary embolism patients, Exp. Gerontol. 69 (2015) 116–121, https://doi.org/10.1016/j.exger.2015.05.007.
[5] R. Rosovsky, J. Borges, C. Kabrhel, K. Rosenfield, Pulmonary embolism response team: inpatient structure, outpatient follow-up, and is it the current standard of care? Clin. Chest Med. 39 (2018) 621–630, https://doi.org/10.1016/j.ccm.2018.04.019.
[6] L. Hobohm, I.T. Farmakis, K. Keller, B. Scibior, A.C. Mavromanoli, I. Sagoschen, T. Munzel, I. Ahrens, S. Konstantinides, Pulmonary embolism response team (PERT) implementation and its clinical value across countries: a scoping review and meta-analysis, Clin. Res. Cardiol. 1–11 (2022), https://doi.org/10.1007/s00392-022-02077-0.
[7] S.V. Konstantinides, G. Meyer, C. Becattini, H. Bueno, G.J. Geersing, V.P. Harjola, M.V. Huisman, M. Humbert, C.S. Jennings, D. Jimenez, et al., 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS), Eur. Heart J. 41 (2020) 543–603, https://doi.org/10.1093/eurheartj/ehz405.
[8] J.A. Heit, Epidemiology of venous thromboembolism, Nat. Rev. Cardiol. 12 (2015) 464–474, https://doi.org/10.1038/nrcardio.2015.83.
[9] P.D. Stein, R.D. Hull, F. Kayali, W.A. Ghali, A.K. Alshab, R.E. Olson, Venous thromboembolism according to age: the impact of an aging population, Arch. Intern. Med. 164 (2004) 2260–2265, https://doi.org/10.1001/archinte.164.20.2260.
[10] K. Keller, J. Beule, M. Coldewey, W. Dippold, J.O. Balzer, Impact of advanced age on the severity of normotensive pulmonary embolism, Heart Vessels 30 (2015) 647–656, https://doi.org/10.1007/s00380-014-0533-4.
[11] H.C. McGill Jr., C.A. McMahan, E.E. Herderick, G.T. Malcom, R.E. Tracy, J. P. Strong, Origin of atherosclerosis in childhood and adolescence, Am. J. Clin. Nutr. 72 (2000) 1307S–S1315.
[12] N. Okumiya, K. Tanaka, K. Ueda, T. Omae, Coronary atherosclerosis and antecedent risk factors: pathologic and epidemiologic study in Hisayama Japan, *Am. J. Cardiol.* 56 (1985) 62–66.
[13] D. Lloyd-Jones, R. Adams, M. Carnethon, G. De Simone, T.B. Ferguson, K. Flegal, E. Ford, K. Furie, A. Go, K. Greenlund, et al., Heart disease and stroke statistics–2009 update: a report from the American heart association statistics committee and stroke statistics subcommittee, Circulation 119 (2009) 480–486, https://doi.org/10.1161/CIRCULATIONAHA.108.191259.
[14] K. Keller, Sarcopenia, Wien. Med. Wochenschr. 169 (2019) 157–172, https://doi.org/10.1007/s10354-018-0618-2.
[15] V. Santilli, A. Bernetti, M. Mangone, M. Paoloni, Clinical definition of sarcopenia, Clin. Cases Miner. Bone Metab. 11 (2014) 177–180.
[16] L.J. Melton 3rd, S. Khosla, C.S. Crowson, M.K. O'Connor, W.M. O'Fallon, B. L. Riggs, Epidemiology of sarcopenia, J. Am. Geriatr. Soc. 48 (2000) 625–630.
[17] S. Nishioka, T. Matsushita, A. Yamanouchi, Y. Okazaki, K. Oishi, E. Nishioka, N. Mori, Y. Tokunaga, S. Onizuka, Prevalence and associated factors of coexistence of malnutrition and sarcopenia in geriatric rehabilitation, Nutrients 13 (2021), https://doi.org/10.3390/nu13113745.
[18] J. Ueshima, K. Maeda, A. Shimizu, T. Inoue, K. Murotani, N. Mori, S. Satake, Y. Matsui, H. Arai, Diagnostic accuracy of sarcopenia by "possible sarcopenia" premiered by the Asian Working Group for Sarcopenia 2019 definition, Arch. Gerontol. Geriatr. 97 (2021) 104484, https://doi.org/10.1016/j.archger.2021.104484.
[19] A.J. Cruz-Jentoft, G. Bahat, J. Bauer, Y. Boirie, O. Bruyere, T. Cederholm, C. Cooper, F. Landi, Y. Rolland, A.A. Sayer, et al., Sarcopenia: revised European consensus on definition and diagnosis, Age Ageing 48 (2019) 16–31, https://doi.org/10.1093/ageing/afy169.
[20] S. Mirzai, B.L. Eck, P.H. Chen, J.D. Estep, W.H.W. Tang, Current approach to the diagnosis of sarcopenia in heart failure: a narrative review on the role of clinical and imaging assessments, Circ. Heart Fail. 15 (2022) e009322.
[21] Y. Boirie, Physiopathological mechanism of sarcopenia, J. Nutr. Health Aging 13 (2009) 717–723, https://doi.org/10.1007/s12603-009-0203-x.
[22] H.J. Meyer, F. Benkert, N. Bailis, M. Lerche, T. Denecke, A. Surov, Low skeletal muscle mass defined by thoracic CT as a prognostic marker in acute pulmonary embolism, Nutrition 98 (2022) 111622, https://doi.org/10.1016/j.nut.2022.111622.
[23] H.J. Meyer, A. Wienke, A. Surov, CT-defined low-skeletal muscle mass as a prognostic marker for survival in prostate cancer: A systematic review and meta-

analysis, Urol. Oncol. 40 (103) (2022), https://doi.org/10.1016/j.urolonc.2021.08.009 e109–103 e116.
[24] 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.
[25] K. Keller, L. Hobohm, T. Munzel, M.A. Ostad, Sex-specific differences regarding seasonal variations of incidence and mortality in patients with myocardial infarction in Germany, Int. J. Cardiol. 287 (2019) 132–138, https://doi.org/10.1016/j.ijcard.2019.04.035.
[26] K. Keller, L. Hobohm, T. Munzel, M.A. Ostad, C. Espinola-Klein, C.J. Lavie, S. Konstantinides, M. Lankeit, Survival benefit of obese patients with pulmonary embolism, Mayo Clin. Proc. 94 (2019) 1960–1973, https://doi.org/10.1016/j.mayocp.2019.04.035.
[27] S.V. Konstantinides, A. Torbicki, G. Agnelli, N. Danchin, D. Fitzmaurice, N. Galie, J.S. Gibbs, M.V. Huisman, M. Humbert, N. Kucher, et al., 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism, Eur. Heart J. 35 (3033–3069) (2014) 3069a–a, https://doi.org/10.1093/eurheartj/ehu283.
[28] S.V. Konstantinides, G. Meyer, C. Becattini, H. Bueno, G.J. Geersing, V.P. Harjola, M.V. Huisman, M. Humbert, C.S. Jennings, D. Jimenez, et al., ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS), Eur. Heart J. 2019 (2019), https://doi.org/10.1093/eurheartj/ehz405.
[29] G.D. Perkins, A.J. Handley, R.W. Koster, M. Castren, M.A. Smyth, T. Olasveengen, K.G. Monsieurs, V. Raffay, J.T. Grasner, V. Wenzel, et al., European resuscitation council guidelines for resuscitation 2015: section 2. adult basic life support and automated external defibrillation, Resuscitation 95 (2015) 81–99, https://doi.org/10.1016/j.resuscitation.2015.07.015.
[30] S. Yuan, S.C. Larsson, Epidemiology of sarcopenia: prevalence, risk factors, and consequences, Metabolism 144 (2023) 155533, https://doi.org/10.1016/j.metabol.2023.155533.
[31] A.J. Cruz-Jentoft, A.A. Sayer, Sarcopenia. *Lancet.* 393 (2019) 2636–2646, https://doi.org/10.1016/S0140-6736(19)31138-9.
[32] P.R. Carvalho do Nascimento, M. Bilodeau, S. Poitras, How do we define and measure sarcopenia? A meta-analysis of observational studies, Age Ageing 50 (2021) 1906–1913, https://doi.org/10.1093/ageing/afab148.
[33] G.A. Kelley, K.S. Kelley, Is sarcopenia associated with an increased risk of all-cause mortality and functional disability? Exp. Gerontol. 96 (2017) 100–103, https://doi.org/10.1016/j.exger.2017.06.008.
[34] J.E. Morley, R.N. Baumgartner, R. Roubenoff, J. Mayer, K.S. Nair, Sarcopenia, J. Lab. Clin. Med. 137 (2001) 231–243, https://doi.org/10.1067/mlc.2001.113504.
[35] J. Lin, E.F. Lopez, Y. Jin, H. Van Remmen, T. Bauch, H.C. Han, M.L. Lindsey, Age-related cardiac muscle sarcopenia: combining experimental and mathematical modeling to identify mechanisms, Exp. Gerontol. 43 (2008) 296–306, https://doi.org/10.1016/j.exger.2007.12.005.
[36] W.J. Evans, What is sarcopenia? *The journals of gerontology Series A, Biol. Sci. Med. Sci.* 50 (1995). Spec No:5-8.
[37] L.V. Thompson, Age-related muscle dysfunction, Exp. Gerontol. 44 (2009) 106–111, https://doi.org/10.1016/j.exger.2008.05.003.
[38] A.J. Cruz-Jentoft, J.P. Baeyens, J.M. Bauer, Y. Boirie, T. Cederholm, F. Landi, F. C. Martin, J.P. Michel, Y. Rolland, S.M. Schneider, et al., Sarcopenia: European consensus on definition and diagnosis: report of the European working group on sarcopenia in older people, Age Ageing 39 (2010) 412–423, https://doi.org/10.1093/ageing/afq034.
[39] R.A. Fielding, B. Vellas, W.J. Evans, S. Bhasin, J.E. Morley, A.B. Newman, G. Abellan van Kan, S. Andrieu, J. Bauer, D. Breuille, et al., Sarcopenia: an undiagnosed condition in older adults. current consensus definition: prevalence, etiology, and consequences. International working group on sarcopenia, J. Am. Med. Dir. Assoc. 12 (2011) 249–256, https://doi.org/10.1016/j.jamda.2011.01.003.
[40] M. Yamada, W.J. Lee, M. Akishita, M. Yang, L. Kang, S. Kim, J.P. Lim, W.S. Lim, R. A. Merchant, T. Ong, et al., Clinical practice for sarcopenia in asia: online survey by the asian working group for sarcopenia, Arch. Gerontol. Geriatr. 115 (2023) 105132, https://doi.org/10.1016/j.archger.2023.105132.
[41] X.M. Yao, B.B. Liu, W.Y. Deng, X.H. Wang, The awareness and knowledge regarding sarcopenia among healthcare professionals: a scoping review, J. Frailty Aging 11 (2022) 274–280, https://doi.org/10.14283/jfa.2022.7.
[42] E. Marty, Y. Liu, A. Samuel, O. Or, J. Lane, A review of sarcopenia: Enhancing awareness of an increasingly prevalent disease, Bone 105 (2017) 276–286, https://doi.org/10.1016/j.bone.2017.09.008.
[43] A.S. Sousa, R.S. Guerra, I. Fonseca, F. Pichel, T.F. Amaral, Sarcopenia and length of hospital stay, Eur. J. Clin. Nutr. 70 (2016) 595–601, https://doi.org/10.1038/ejcn.2015.207.
[44] J. Pacifico, M.A.J. Geerlings, E.M. Reijnierse, C. Phassouliotis, W.K. Lim, A. B. Maier, Prevalence of sarcopenia as a comorbid disease: a systematic review and meta-analysis, Exp. Gerontol. 131 (2020) 110801, https://doi.org/10.1016/j.exger.2019.110801.
[45] M.R. Jaff, M.S. McMurtry, S.L. Archer, M. Cushman, N. Goldenberg, S. Z. Goldhaber, J.S. Jenkins, J.A. Kline, A.D. Michaels, P. Thistlethwaite, et al., Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American heart association, Circulation 123 (2011) 1788–1830, https://doi.org/10.1161/CIR.0b013e318214914f.
[46] M. Martinho, R. Cale, J. Grade Santos, A. Rita Pereira, S. Alegria, F. Ferreira, M. Jose Loureiro, T. Judas, M. Ferreira, A. Gomes, et al., Underuse of reperfusion therapy with systemic thrombolysis in high-risk acute pulmonary embolism in a Portuguese center, Rev. Port. Cardiol. 43 (2024) 55–64, https://doi.org/10.1016/j.repc.2023.07.005.
[47] P.D. Stein, F. Matta, Thrombolytic therapy in unstable patients with acute pulmonary embolism: saves lives but underused, Am. J. Med. 125 (2012) 465–470, https://doi.org/10.1016/j.amjmed.2011.10.015.
[48] L. Hobohm, I.T. Farmakis, D. Duerschmied, K. Keller, The current evidence of pulmonary embolism response teams and their role in future, Hamostaseologie (2024), https://doi.org/10.1055/a-2232-5395.
[49] D. Bertschi, C.M. Kiss, N. Beerli, O. Mauthner, R.W. Kressig, Impact of sarcopenia on daily functioning: a cross-sectional study among older inpatients, Aging Clin. Exp. Res. 34 (2022) 2041–2046, https://doi.org/10.1007/s40520-022-02175-z.
[50] S. Kakehi, H. Wakabayashi, H. Inuma, T. Inose, M. Shioya, Y. Aoyama, T. Hara, K. Uchimura, K. Tomita, M. Okamoto, et al., Rehabilitation nutrition and exercise therapy for sarcopenia, World J. Mens Health. 40 (2022) 1–10, https://doi.org/10.5534/wjmh.200190.
[51] M. Tohyama, Y. Shirai, Y. Kokura, R. Momosaki, Nutritional care and rehabilitation for frailty, sarcopenia, and malnutrition, Nutrients (2023) 15, https://doi.org/10.3390/nu15234908.