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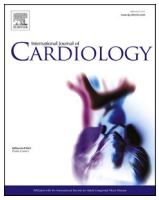

Cardiovascular comorbidities predict mortality in acute pancreatitis

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ABSTRACT

Background: The in-hospital mortality of acute pancreatitis (AP) is determined by severity of AP, but also significantly impacted by patients' comorbidities. Therefore, we aimed to examine the association between comorbid risk-profiles and survival in hospitalized patients admitted with AP.

Methods: We utilized the German nationwide inpatient statistics to identify all AP patient-cases (ICD code K85) admitted to hospitals in Germany between 2005 and 2019. Hospitalization cases for AP were stratified by survival, and risk factors for in-hospital mortality were examined.

Results: In total, 797,364 hospitalization-cases of patients admitted due to AP (median age 56.0 [IQR 44.0–71.0] years, 39.2 % females) were treated in Germany 2005–2019. Of these, 22,022 (2.8 %) patients died during hospitalization. AP survivors were younger (56.0 [44.0–71.0] vs. 76.0 [64.0–84.0], $P < 0.001$), more often males (61.0 % vs. 54.1 %, $P < 0.001$), and were less often afflicted by cardiovascular risk factors and diseases than non-survivors. Cardiovascular diseases (OR 2.08 (95 %CI 2.02–2.15), $P < 0.001$) and raising number of cardiovascular diseases (OR 1.48 (95 %CI 1.45–1.50), $P < 0.001$) were independently associated with increasing mortality. In particular, heart failure (OR 2.16 [95 %CI 2.09–2.24], $P < 0.001$), peripheral artery disease (OR 1.25 [1.15–1.35], $P < 0.001$), atrial fibrillation/flutter (OR 1.61 [95 %CI 1.55–1.66], $P < 0.001$), myocardial infarction (OR 4.71 [95 %CI 4.28–5.18], $P < 0.001$), pulmonary embolism (OR 12.19 [95 %CI 10.91–13.62], $P < 0.001$), and stroke (OR 7.21 [95 %CI 6.42–8.11], $P < 0.001$) were independently associated with in-hospital mortality.

Conclusions: Between 2005 and 2019, the in-hospital mortality among hospitalized AP patients was 2.8 % in Germany. Presence of cardiovascular diseases was associated with significantly reduced survival in AP patients.

1. Introduction

Acute pancreatitis (AP) is a major health care problem with increasing incidence worldwide [1–6]. In Western countries the incidence ranges between 13 and 100 patients per 100,000 population [7], while an incidence between 13 and 43 individuals per 100,000 inhabitants was reported for Germany [8–10]. Pathophysiologically, the majority of AP cases are caused by alcohol consumption and gallstones followed by rarer causes such as hypertriglyceridaemia, AP after endoscopic retrograde cholangiopancreatography, and medication-induced AP [7,11–13]. While approximately 4/5 of the AP events are of a mild character and resolve with only supportive treatment, 1/5 of AP patients develop a severe AP, which is associated with complications as well as increased morbidity and mortality [14–21]. Risk stratification tools are established for prognosis prediction [6,9,14–16,18,22–26] showing that organ failure, local and systemic complications including peritonitis, venous thromboembolism, systemic inflammatory response syndrome (SIRS), sepsis and particularly pancreatic necrosis are related to poor outcome [6,23,27]. While mild AP cases are afflicted by a low mortality rate of approximately 0.1 %, the mortality increases to 54.1 % in patients with critical AP manifestation [16–21]. Besides the severity of AP, the individual comorbidity profile of each patient might also represent an important factor to withstand and resist the acute stress of AP and may help to avoid aggravation of AP from mild to severe forms. Several

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studies have reported an important impact of the patients' individual comorbidity profile on outcome of different diseases [28–41]. Research results of population-based studies indicate for an association between cardiovascular disease and acute pancreatitis and especially, ischemic heart disease and hypertension seem to influence and increase the risk of acute pancreatitis [40]. In addition, available evidence indicates also for an association between history of acute pancreatitis and increased risk for development of atherosclerotic cardiovascular diseases and their acute manifestations [41,42]. Thus, the primary objective of this present study was to identify parameters of the patient characteristics and co-morbidity burden independently impacting the survival of AP. This risk stratification might help to categorize AP patients' risk regarding short-term in-hospital mortality more precisely.

2. Methods

In Germany, a new remuneration system for all treated patients for coexisting conditions, surgeries, interventions, treatments and procedures was implemented in the year 2004. This remuneration system is based on coding of these coexisting conditions, surgeries, interventions, treatments and procedures of the treated patients, which have to be coded by the German hospitals and afterwards have to be transferred to the Institute for the Hospital Remuneration System as well as the Federal Statistical Office of Germany (Statistisches Bundesamt) in order to receive the remuneration for the provided health care services [43]. Coding has to be carried out according the ICD-10-GM (International Classification of Diseases, 10th Revision with German Modification) and surgical, diagnostic and interventional procedures were coded with OPS codes (Operationen- und Prozedurenschlüssel) [43]. The Federal Statistical Office of Germany gathers all mentioned codes of the hospitalized patient-cases and included them in the German nationwide inpatient statistics. These gathered data could be used for research purposes (diagnosis related groups [DRG] statistic) and has been used by us for our present study-analysis [43]. Thus, this dataset comprises as the German nationwide inpatient statistics nearly all hospitalizations of patients in German hospitals. Only a very small minority of psychiatric patients and patients of the German federal army are not included in this dataset, but the total number of these not included patients is very very small in comparison to the very large dataset of the German nationwide inpatient statistics.

For our analysis, we generated a statistical syntax and sent this syntax to the Research Data Center (RDC) of the Statistical Offices of the federal states (in Wiesbaden, Germany), which computed the study results on our behalf based on our generated and delivered syntaxes. For the present study, we selected and included all inpatients hospitalized due to an AP (all inpatients with a main diagnosis of AP [ICD code K85]) (source: RDC of the Federal Statistical Office and the Statistical Offices of the federal states, DRG Statistics 2005–2019, own calculations). The main diagnosis of each patient is defined as the diagnosis, which is/was mainly responsible for the hospitalization documented by the hospital (discharging physician). The AP (ICD code K85) patient-cases were stratified according survival and survivors versus non-survivors were compared.

2.1. Study endpoints

The primary study endpoint was death of all-causes during the in-hospital stay (in-hospital death).

2.2. Definitions

Obesity is defined as body mass index $\geq$30 kg/m^2 according to the World Health Organization (WHO) [44]. Shock and cardio-pulmonary resuscitation were defined according to current European guidelines [45–47]. Pancreas specific surgeries comprised the OPS code 5–52.

2.3. Ethical aspects and study oversight

The present study did not comprise a direct access by us (as the investigators) to data of individual patients, but only to aggregated results provided by the RDC. Thus, approval by an ethics committee and informed consent were not required, in compliance with German law.

2.4. Statistics

Descriptive statistics for the comparison of AP patients, who survived (survivors) or died during hospital stay (non-survivors) were performed with median and interquartile range (IQR), or absolute numbers and corresponding percentages. Whereas continuous variables were compared with the use of the Wilcoxon-Whitney *U* test, the comparison of categorical variables was computed with Fisher's exact or chi^2 test, as appropriate.

Logistic regression models were calculated to investigate the impact of different parameters of patients' characteristics, conditions and comorbidities as well as adverse in-hospital events on patients' survival. Results were presented as odds ratios (OR) and related 95 % confidence intervals (CI). In order to ensure that the results of these logistic regressions are not substantially confounded by age, sex and important comorbidities influencing survival, the multivariable logistic regressions were adjusted for these aforementioned parameters. The logistic regressions were calculated with all of the parameters in one model and the adjustment comprised the following parameters: age, sex, obesity, cancer, heart failure, essential arterial hypertension, chronic kidney disease (CKD, chronic kidney disease stages 3 to 5 with glomerular filtration rate < 60 ml/min/1.73 m^2), diabetes mellitus, coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), and atrial fibrillation/flutter (AF). Moreover, a receiver operating curve (ROC) analysis was performed to analyse the effect of an increasing number of cardiovascular risk factors and/or cardiovascular diseases for prediction of in-hospital mortality.

The software of SPSS® (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp) was used for the computerised data analysis. *P* values lower than 0.05 (two-sided) were considered to be statistically significant.

3. Results

In total, 797,364 hospitalization-cases of patients admitted due to AP (median age 56.0 [IQR 44.0–71.0] years, 39.2 % females) were treated in Germany between the years 2005 and 2019 and were included in the present study. Of these, 22,022 (2.8 %) patients died during the hospitalization. Overall, 78,437 (9.8 %) were treated on ICU.

AP survivors were in median 20 years younger (56.0 [44.0–71.0] vs. 76.0 [64.0–84.0], $P < 0.001$), more often males (61.0 % vs. 54.1 %, $P < 0.001$), less often obese (7.3 % vs. 8.5 %, $P < 0.001$) and were less often afflicted by cardiovascular risk factors such as arterial hypertension (39.4 % vs. 41.5 %, $P < 0.001$) and diabetes mellitus (18.4 % vs. 26.8 %, $P < 0.001$) (Table 1).

Non-survivors bear higher rates of cardiovascular risk factors (58.2 % vs. 51.7 %, $P < 0.001$) as well as substantially higher frequency of cardiovascular diseases (49.4 % vs. 17.5 %, $P < 0.001$). In detail, the cardiovascular comorbidities CAD (16.8 % vs. 8.7 %, $P < 0.001$), heart failure (26.4 % vs. 5.8 %, $P < 0.001$), peripheral artery disease (3.2 % vs. 1.4 %, $P < 0.001$) and AF (25.5 % vs. 7.1 %, $P < 0.001$) were more prevalent in non-survivors (Table 1). As shown in Fig. 1, in-hospital mortality rate increases with raising number of cardiovascular risk factors and/or cardiovascular disease.

In addition, COPD (8.8 % vs. 4.0 %, $P < 0.001$) as well as CKD (16.6 % vs. 4.7 %, $P < 0.001$) were diagnosed more frequently in the deceased patients (Table 1).

We detected acute manifestations of cardiovascular diseases such as myocardial infarction (3.0 % vs. 0.3 %, $P < 0.001$), stroke (2.0 % vs. 0.2

Table 1
Patients' characteristics, medical history, presentation and outcomes of the included 797,364 patients with acute pancreatitis stratified for survival.

Parameters	Survivors (n = 775,342; 97.2 %)	Non-survivors (n = 22,022; 2.8 %)	P-value
Age	56.0 (44.0–71.0)	76.0 (64.0–84.0)	**<0.001**
Age ≥ 70 years	206,967 (26.7 %)	14,466 (65.7 %)	**<0.001**
Female sex	302,230 (39.0 %)	10,106 (45.9 %)	**<0.001**
In-hospital stay (days)	8.0 (5.0–12.0)	10.0 (3.0–24.0)	**<0.001**
Prolonged in-hospital stay >14 days	133,617 (17.2 %)	8631 (39.2 %)	**<0.001**
Traditional cardiovascular risk factors			
Obesity	56,744 (7.3 %)	1866 (8.5 %)	**<0.001**
Essential arterial hypertension	305,800 (39.4 %)	9132 (41.5 %)	**<0.001**
Diabetes mellitus	142,751 (18.4 %)	5893 (26.8 %)	**<0.001**
Hyperlipidaemia	87,156 (11.2 %)	1873 (8.5 %)	**<0.001**
Cardiovascular risk factors (at least one of the investigated cardiovascular risk factors)	401,176 (51.7 %)	12,827 (58.2 %)	**<0.001**
Surgery			
Any surgery	516,268 (66.6 %)	16,334 (74.2 %)	**<0.001**
Pancreas surgery	34,301 (4.4 %)	4056 (18.4 %)	**<0.001**
Comorbidities			
Coronary artery disease	67,774 (8.7 %)	3705 (16.8 %)	**<0.001**
Heart failure	44,925 (5.8 %)	5824 (26.4 %)	**<0.001**
Peripheral artery disease	11,230 (1.4 %)	695 (3.2 %)	**<0.001**
Atrial fibrillation/flutter	55,111 (7.1 %)	5607 (25.5 %)	**<0.001**
Cardiovascular diseases (at least one of the investigated cardiovascular diseases)	135,867 (17.5 %)	10,889 (49.4 %)	**<0.001**
Cardiovascular diseases or cardiovascular risk factors (at least one of the investigated cardiovascular risk factors or diseases)	430,373 (55.5 %)	16,371 (74.3 %)	**<0.001**
Chronic obstructive pulmonary disease	31,120 (4.0 %)	1943 (8.8 %)	**<0.001**
Chronic kidney disease (chronic kidney disease stages 3 to 5 with glomerular filtration rate < 60 ml/min/1.73 m^2)	36,436 (4.7 %)	3657 (16.6 %)	**<0.001**
Cancer	16,754 (2.2 %)	1190 (5.4 %)	**<0.001**
Liver diseases	106,738 (13.8 %)	4382 (19.9 %)	**<0.001**
Chronic anemia	37,456 (4.8 %)	3668 (16.7 %)	**<0.001**
Thrombophilia	689 (0.1 %)	76 (0.3 %)	**<0.001**
Adverse events during hospitalization			
Myocardial infarction	2157 (0.3 %)	662 (3.0 %)	**<0.001**
Tachycardia	3717 (0.5 %)	843 (3.8 %)	**<0.001**
Syncope	3319 (0.4 %)	176 (0.8 %)	**<0.001**
Shock	4505 (0.6 %)	5613 (25.5 %)	**<0.001**
Cardio-pulmonary resuscitation	1443 (0.2 %)	3900 (17.7 %)	**<0.001**
Deep venous thrombosis and/or thrombophlebitis	11,884 (1.5 %)	767 (3.5 %)	**<0.001**
Pulmonary embolism	1250 (0.2 %)	551 (2.5 %)	**<0.001**
Cardiovascular diseases or their acute manifestations or cardiovascular risk factors (at least one of these conditions)	435,634 (56.2 %)	16,852 (76.5 %)	**<0.001**
Sepsis	5200 (0.7 %)	1893 (8.6 %)	**<0.001**
Hepatitis	5344 (0.7 %)	148 (0.7 %)	0.761
Urinary tract infection	32,008 (4.1 %)	2084 (9.5 %)	**<0.001**
Pneumonia	28,388 (3.7 %)	5392 (24.5 %)	**<0.001**
Acute kidney injury	23,932 (3.1 %)	10,303 (46.8 %)	**<0.001**
Stroke (ischaemic or haemorrhagic)	1278 (0.2 %)	448 (2.0 %)	**<0.001**
Gastro-intestinal bleeding	7917 (1.0 %)	1081 (4.9 %)	**<0.001**
Intracranial bleeding	91 (0.01 %)	71 (0.32 %)	**<0.001**
Necessity for transfusion of blood constituents	29,525 (3.8 %)	8962 (40.7 %)	**<0.001**

%, P < 0.001), pulmonary embolism (2.5 % vs. 0.2 %, $P < 0.001$), and deep venous thrombosis or thrombophlebitis (3.5 % vs. 1.5 %, $P < 0.001$) more often in non-survivors (Table 1). Moreover, acute infections such as sepsis, pneumonia and all bleeding complications were more prevalent in non-survivors than in survivors (Table 1).

Corresponding to higher proportion of severe AP, pancreas surgery was more often performed in non-survivors than in survivors (18.4 % vs. 4.4 %, $P < 0.001$) (Table 1).

Independent risk factors for mortality in AP patients with focus on the patients' characteristics are older age (OR 1.06 [95 %CI 1.05–1.06], $P < 0.001$) and especially age ≥ 70 years (OR 3.86 [95 %CI 3.74–3.99], $P < 0.001$), male sex (OR 1.16 [95 %CI 1.12–1.19], P < 0.001), obesity (OR 1.27 [95 %CI 1.22–1.35], P < 0.001), and diabetes mellitus (OR 1.13 [95 %CI 1.09–1.17], P < 0.001), but not the cardiovascular risk factors arterial hypertension and hyperlipidaemia (Table 2).

Regarding cardiovascular comorbidities, heart failure (OR 2.16 [95 %CI 2.09–2.24], $P < 0.001$), peripheral artery disease (OR 1.25 [1.15–1.35], P < 0.001), and AF (OR 1.61 [95 %CI 1.55–1.66], $p < 0.001$) were independent risk factors for mortality, while CAD was not an independent risk factor for in-hospital death (Table 2, Fig. 2). COPD (OR 1.29 [95 %CI 1.23–1.36], $P < 0.001$), CKD (OR 1.41 [95 %CI 1.35–1.47], P < 0.001) as well as cancer (OR 1.77 [95 %CI 1.67–1.89], P < 0.001) were further strong and independent risk factors for the AP patients to die during in-hospital course.

An increasing number of cardiovascular risk factors and/or cardiovascular diseases was significantly associated with an increased mortality (univariable: OR 1.41 (95 %CI 1.39–1.42), $P < 0.001$; multivariable: OR 1.05 (95 %CI 1.04–1.06), P < 0.001) independently of age, sex, cancer, chronic kidney disease (chronic kidney disease stages 3 to 5 with glomerular filtration rate < 60 ml/min/1.73 m^2), and chronic obstructive pulmonary disease. In particular, a the presence of cardiovascular diseases (at least one cardiovascular disease) was independently associated with higher mortality (univariable: OR 4.60 (95 %CI 4.48–4.73), $P < 0.001$; multivariable: OR 2.08 (95 %CI 2.02–2.15), P < 0.001) as well as a raising number of cardiovascular diseases were related to and increasing in-hospital mortality (univariable: OR 2.33 (95 %CI 2.30–2.36), P < 0.001; multivariable: OR 1.48 (95 %CI 1.45–1.50), P < 0.001) independently of age, sex, obesity, cancer, essential arterial hypertension, chronic kidney disease (chronic kidney disease stages 3 to 5 with glomerular filtration rate < 60 ml/min/1.73 m^2), diabetes mellitus, and chronic obstructive pulmonary disease (Fig. 3).

The ROC curve showed an area under the curve of 0.63 (95 %CI 0.62–0.63, P < 0.001) for an increasing number of cardiovascular risk factors and/or cardiovascular diseases to predict in-hospital mortality in AP patients (Fig. 4).

Annual trends regarding the prevalence of cardiovascular risk factors as well as cardiovascular diseases in patients admitted due to acute

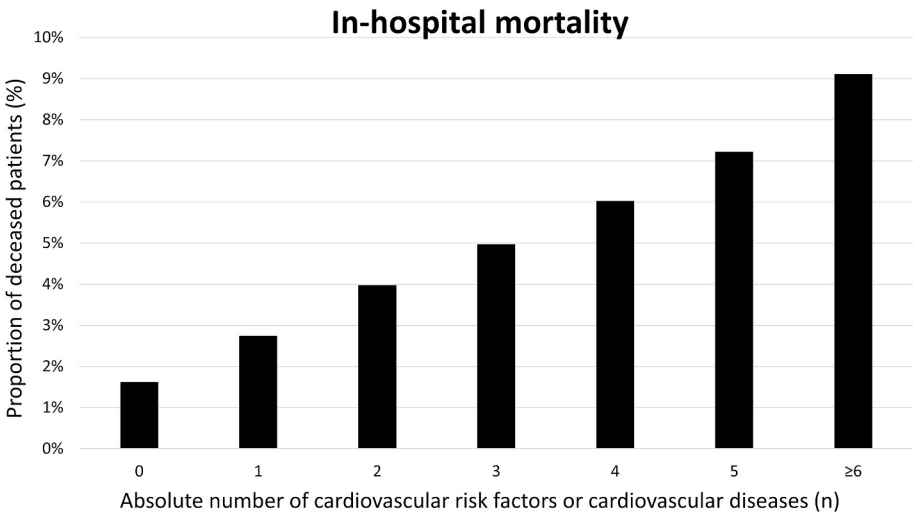

Fig. 1. Absolute number of cardiovascular risk factors or cardiovascular diseases and related in-hospital mortality rate.

Table 2
Risk factors for in-hospital mortality in patients with acute pancreatitis (univariable and multivariable logistic regression models).

	Univariable regression model		Multivariable regression model*	
	OR (95 % CI)	P-value	OR (95 % CI)	P-value
Age	1.06 (1.06–1.06)	**<0.001**	1.06 (1.05–1.06)	**<0.001**
Age ≥ 70 years	5.26 (5.11–5.41)	**<0.001**	3.86 (3.74–3.99)	**<0.001**
Female sex	1.33 (1.29–1.36)	**<0.001**	0.86 (0.84–0.89)	**<0.001**
Traditional cardiovascular risk factors				
Obesity	1.17 (1.12–1.23)	**<0.001**	1.27 (1.22–1.35)	**<0.001**
Essential arterial hypertension	1.09 (1.06–1.12)	**<0.001**	0.59 (0.57–0.60)	**<0.001**
Diabetes mellitus	1.62 (1.57–1.67)	**<0.001**	1.13 (1.09–1.17)	**<0.001**
Hyperlipidaemia	0.73 (0.70–0.77)	**<0.001**	0.56 (0.53–0.59)	**<0.001**
Surgery				
Any surgery	1.44 (1.40–1.49)	**<0.001**	1.15 (1.11–1.18)	**<0.001**
Pancreas surgery	4.88 (4.71–5.06)	**<0.001**	5.13 (4.94–5.33)	**<0.001**
Comorbidities				
Coronary artery disease	2.11 (2.04–2.19)	**<0.001**	0.91 (0.88–0.95)	**<0.001**
Heart failure	5.85 (5.67–6.03)	**<0.001**	2.16 (2.09–2.24)	**<0.001**
Peripheral artery disease	2.22 (2.05–2.40)	**<0.001**	1.25 (1.15–1.35)	**<0.001**
Atrial fibrillation/flutter	4.46 (4.33–4.61)	**<0.001**	1.61 (1.55–1.66)	**<0.001**
Chronic obstructive pulmonary disease	2.31 (2.21–2.43)	**<0.001**	1.29 (1.23–1.36)	**<0.001**
Chronic kidney diesease (chronic kidney disease stages 3 to 5 with glomerular filtration rate < 60 ml/min/1.73 m^2)	4.04 (3.89–4.19)	**<0.001**	1.41 (1.35–1.47)	**<0.001**
Cancer	2.59 (2.44–2.75)	**<0.001**	1.77 (1.67–1.89)	**<0.001**
Liver disease	1.56 (1.50–1.61)	**<0.001**	2.09 (2.02–2.17)	**<0.001**
Chronic anemia	3.94 (3.79–4.09)	**<0.001**	2.84 (2.73–2.95)	**<0.001**
Thrombophilia	3.89 (3.07–4.94)	**<0.001**	4.10 (3.19–5.28)	**<0.001**
Adverse events during hospitalization				
Myocardial infarction	11.11 (10.17–12.13)	**<0.001**	4.71 (4.28–5.18)	**<0.001**
Shock	58.53 (56.12–61.05)	**<0.001**	59.49 (56.70–62.42)	**<0.001**
Tachycardia	8.26 (7.66–8.92)	**<0.001**	5.48 (5.04–5.95)	**<0.001**
Syncope	1.87 (1.61–2.18)	**<0.001**	1.12 (0.96–1.31)	0.157
Cardio-pulmonary resuscitation	115.42 (108.46–122.82)	**<0.001**	126.13 (117.64–135.24)	**<0.001**
Deep venous thrombosis and/or thrombophlebitis	2.32 (2.15–2.50)	**<0.001**	2.69 (2.49–2.91)	**<0.001**
Pulmonary embolism	15.89 (14.36–17.58)	**<0.001**	12.19 (10.91–13.62)	**<0.001**
Sepsis	13.93 (13.19–14.71)	**<0.001**	13.73 (12.92–14.58)	**<0.001**
Hepatitis	0.98 (0.83–1.15)	0.761	1.84 (1.55–2.18)	**<0.001**
Urinary tract infection	2.43 (2.32–2.54)	**<0.001**	1.37 (1.30–1.44)	**<0.001**
Pneumonia	8.53 (8.26–8.82)	**<0.001**	5.99 (5.78–6.21)	**<0.001**
Acute kidney injury	27.60 (26.80–28.43)	**<0.001**	20.15 (19.52–20.80)	**<0.001**
Stroke (ischaemic or haemorrhagic)	12.58 (11.29–14.02)	**<0.001**	7.21 (6.42–8.11)	**<0.001**
Gastro-intestinal bleeding	5.00 (4.69–5.34)	**<0.001**	3.92 (3.66–4.21)	**<0.001**
Intracranial bleeding	27.56 (20.20–37.59)	**<0.001**	27.37 (19.42–38.58)	**<0.001**
Necessity for transfusion of blood constituents	17.33 (16.83–17.85)	**<0.001**	14.55 (14.09–15.02)	**<0.001**

* Adjusted for age, sex, obesity, cancer, heart failure, essential arterial hypertension, chronic kidney disease (chronic kidney disease stages 3 to 5 with glomerular filtration rate < 60 ml/min/1.73 m^2), diabetes mellitus, coronary artery disease, chronic obstructive pulmonary disease, and atrial fibrillation/flutter.

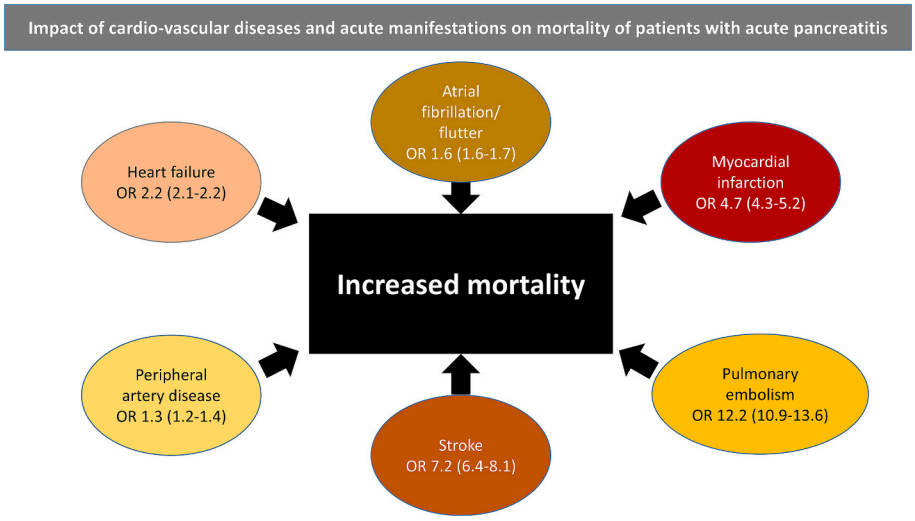

Fig. 2. and graphical abstract: Impact of cardiovascular diseases on in-hospital mortality of AP.

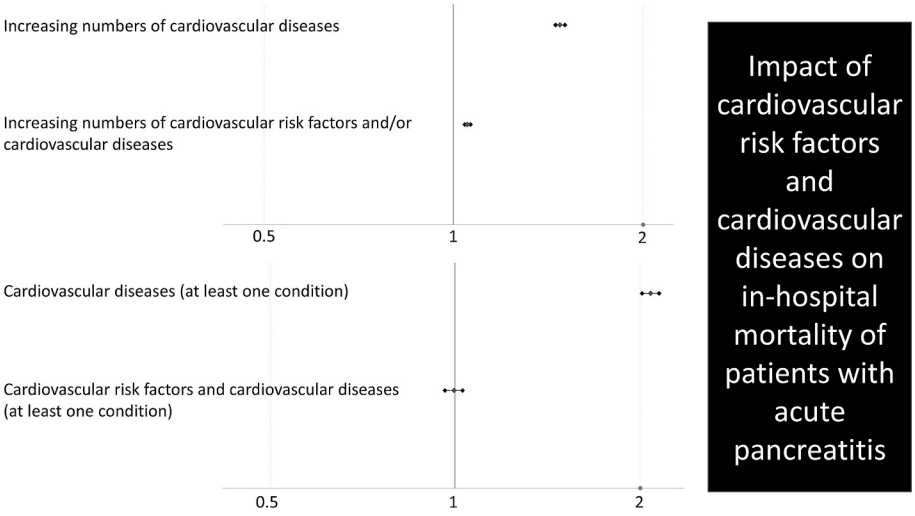

Fig. 3. Impact of cardiovascular risk factors and cardiovascular diseases on in-hospital mortality of patients with acute pancreatitis.

pancreatitis revealed an increasing prevalence of these cardiovascular conditions in patients with acute pancreatitis and emphasize the importance of cardiovascular risk factors as well as cardiovascular diseases in patients admitted due to acute pancreatitis (Fig. 5).

All analysed adverse events during hospitalization were associated with an increased mortality (Table 2). Acute cardiovascular, renal and infectious manifestations were in addition with bleeding events independently related to highly increased mortality.

4. Discussion

Acute pancreatitis (AP) is a major public health concern worldwide [1–6]. Global incidence of AP increased during the last decades [1–3,8–10]. The initial phase of AP is characterized by (localized) inflammation comprising cytokine release, leukocyte activation, and an increase of oxidative stress. Further aggravation is afflicted by systemic inflammatory response syndrome (SIRS) and development of severe AP with complications such as hypovolemic and distributive shock and multi-organ failure or damage [6,48]. In this context, interleukin 6 (IL-6) is one of the most important cytokines involved in the disease course of AP, starting in cellular injury, substantially continuing to inflammatory response and contributing to (multi-)organ involvement, complications and severity status of AP [49,50].

The in-hospital mortality rate in our study of all hospitalized AP patient-cases in Germany was 2.8 %. This overall mortality of the AP patients is comparable with published studies (approximately 2 %). It is substantially affected by comorbidities and severity of AP. In severe AP the mortality increases to more than 30 % [10,16–21].

The primary objective of our present study was to identify parameters of the patients' characteristics and comorbidity burden independently impacting the survival of AP. We detected a strong independent impact of cardiovascular diseases such as heart failure, peripheral artery disease, AF, and the acute cardiovascular manifestations myocardial infarction, stroke and pulmonary embolism on survival of AP patients. Cardiovascular risk factors as well as cardiovascular diseases and their acute manifestations were substantially more prevalent in non-survivors than in AP patients who survived. The presence of at least one cardiovascular disease was associated with 2.1-fold increased risk to die during in-hospital stay. An increasing number of cardiovascular diseases affected the mortality of AP patients with a 1.5-fold higher mortality-rate per additional cardiovascular disease in the comorbidity profile of the AP patients. Thus, our study results indicate for an interplay between cardiovascular diseases and AP and underline the importance of cardiovascular risk factors and diseases regarding the mortality of AP

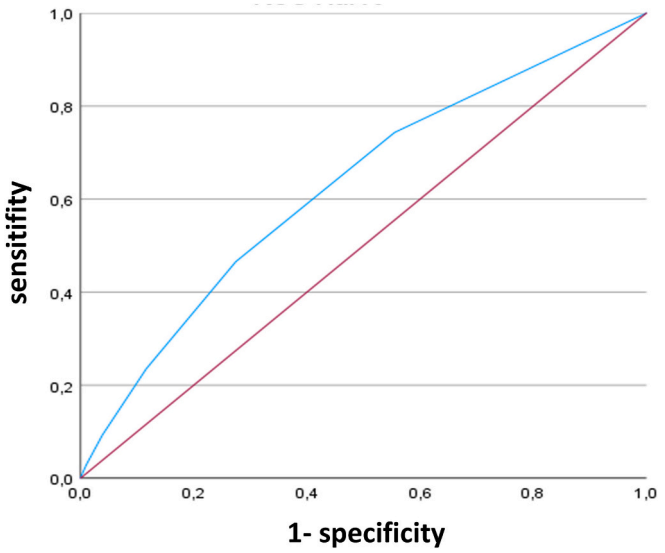

Fig. 4. Receiver operating curve (ROC) to analyse the effect of an increasing number of cardiovascular risk factors and/or cardiovascular diseases for prediction of in-hospital mortality.

patients in concordance with other studies [40,41]. While studies revealed that CAD and arterial hypertension were related to increase the incidence of AP [40] and longitudinal studies reported that history of AP was associated with an increased risk of acute atherosclerotic cardiovascular disease and acute coronary syndrome in the future [41]. In patients with severe AP, cardiovascular diseases and acute cardiovascular deviations/manifestations comprising abnormalities of cardiac rhythm, contractility, and vasomotor tone of peripheral vessels are influencing patients' prognosis [51]. In this context, AP related hypovolemia as well as metabolic disturbances such as hyperkalemia, hypomagnesemia, and hypophosphatemia may result in hypotension, tachycardia, and signs of SIRS and can aggravate cardiovascular diseases [51]. The results of our study support the assumption that the interplay of AP and cardiovascular diseases is not limited to the influence on their mutual influence of each other, but nearly all investigated cardiovascular diseases have a substantial impact on survival of AP patients. Vice versa, a history of AP seems to increase the risk to develop atherosclerotic cardiovascular diseases and their acute manifestations [41,42]. The rising frequency of cardiovascular risk factors and cardiovascular diseases in AP patients emphasized the importance of an optimal management of these conditions to prevent in-hospital death of AP patients. In addition, it would be of interest to study the impact of AP on cardiovascular risk in populations with very low levels of cardiovascular risk and low prevalence of CAD [52]. The results of our study revealed a strong and independent impact of pulmonary embolism on increased mortality, which is in accordance with previously published studies [6,53–56]. Since PE is afflicted by a substantial increase of mortality, the awareness for VTE events in AP should be significantly inclined [3,6,57].

Additionally, an early onset of organ dysfunction and especially of concomitant cardiovascular diseases is associated with reduced survival, which highlights the importance of an optimal management of cardiovascular comorbidities and avoidance of exacerbations of cardiovascular disease in AP [51,58].

Besides cardiovascular comorbidities and deviations, other comorbidities concerning different organ systems such as the lungs, kidneys as well as bleeding events, cancer and metabolic and infectious deviations in different locations have a significant impact on survival.

Metabolic abnormalities such as obesity and diabetes mellitus are key contributing factors for poor prognosis in AP patients, which is in accordance with previously published studies [32–35,59]. In line with the study of Martinez et al. obesity was a risk factor for mortality of AP in our present study-findings [59]. Moreover, it is well known that diabetes mellitus is related to higher incidence of AP [33,36–38] and our results confirmed that diabetes mellitus is also negatively associated with survival of AP patients [39]. Additionally, diabetes mellitus influences the development of kidney failure. A large meta-analysis indicated that approximately 25 %–50 % of the AP patients with a co-prevalence of diabetes mellitus were afflicted by kidney diseases and kidney failure affected the survival negatively [39]. In line with these results, our study demonstrated that chronic and especially acute kidney impairment were associated with increased mortality. Lung diseases and respiratory deviations as well as infections such as pneumonia and sepsis were associated with higher mortality as in the literature [60]. In particular, systemic inflammatory response syndrome (SIRS) and sepsis are in part directly related to pancreatic necrosis affecting outcome substantially and negatively [6,23,27]. In this context, severe AP develops in the majority of cases a pro-inflammatory response resulting in SIRS, while sepsis or infection only rarely occurs. Nevertheless, if the SIRS is severe or sepsis occurs, then proinflammatory mediators can cause early multiple organ failure involving several organ systems with respiratory, cardiovascular, renal, and hepatic failure [61]. In contrast to the literature, the sepsis rate in our study seems higher than the incidence in the

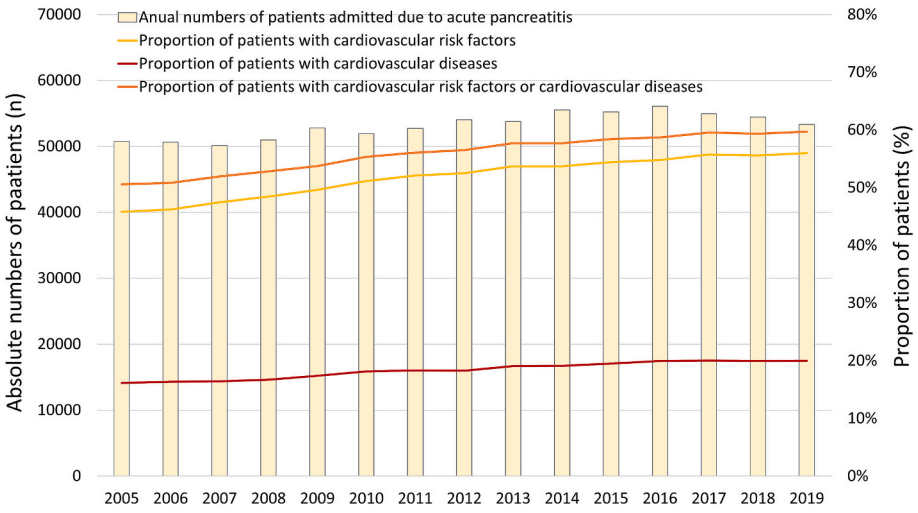

Fig. 5. Annual trends regarding absolute numbers of patient-cases of patients admitted due to acute pancreatitis as well as regarding proportions of cardiovascular risk factors and cardiovascular diseases.

already published literature [61]. Nevertheless, the higher rate of sepsis in deceased AP patients is a clear indicator for a higher rate of severe AP in the non-survivors.

In addition, bleeding complications were strong predictors of mortality in AP patients [62]. Our study revealed that cancer influenced mortality of AP patients negatively as well. In this context, it has to be mentioned that studies have shown that AP might be an early symptom of pancreatic cancer [63,64]. In addition and as expected, pancreatic surgery as a treatment of severe AP with necrosis, was strongly associated increased mortality [14–21]. Although the treatment progress resulted in a further decrease of the overall mortality rate during the last decades [21,23], the mortality of severe AP is still high in patients with severe AP amounting 21–40 % in the United States and the European Union [65].

The results of our study highlight the importance of the precise taking into account of the individual comorbidity burden and providing adequate treatment of the patients' comorbidity profile in order to optimize the management of AP [32–34]. Besides the optimal management of the AP and its complications, our study results emphasize that the optimization and management of the cardiovascular diseases is also of outstanding importance to prevent in-hospital death. AP acts as a potential stressor for the cardiovascular system affecting, aggravating and potentially manifesting imminent or existing cardiovascular diseases. Optimization of fluid status for AP and optimization of treatment strategies regarding cardiovascular diseases might decrease the stress caused by AP on cardiovascular system. For health care planning in the German health care systems, early risk stratification, the identification of these important comorbidities and their optimal management is critical, since intensive care and hospital capacities are bottlenecks of optimal management. [14,35,58,66]

5. Limitations

Several limitations of our study must be considered: I) the study is based on ICD and OPS codes of German hospitalized patients. This epidemiological approach of the nationwide inpatient statistics might make the data prone for under-reporting or under-coding. II) Due to the character of the German nationwide inpatient statistics, we were only able to provide data for the in-hospital course, but no data regarding later follow-up. III) The AP severity and AP aetiology could not be encompassingly detected with this data. IV) Especially, laboratory markers and results of radiological examinations regarding necrosis are missing. Therefore, the established prognostic scoring systems based on imaging, clinical and laboratory chemical tests for prediction of the severity of AP could not be calculated [6,14–16,18,22–24,27]. V) The German nationwide inpatients statistics does not have included information on ethnicity. Therefore, the transfer of the study results to countries with other populations might be difficult. VI) Finally, we could not distinguish the included hospitalized patient-cases of our study regarding first admission or recurrent admission of the same patient.

6. Conclusions

During the time-period 2005–2019 the mortality rate of AP patients was 2.8 % regarding all hospitalized AP patient-cases in Germany. Especially, cardiovascular risk factors, comorbidities and their acute manifestations were accompanied by reduced survival of AP patients.

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. **Lukas Hobohm:** Writing – review & editing, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Volker H. Schmitt:** Writing – review & editing. **Omar Hahad:** Writing – review & editing. **Christian Labenz:** Writing – review & editing. **Christine Espinola-Klein:** Writing – review & editing. **Markus Möhler:** Writing – review & editing. **Visvakanth Sivanathan:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

KK, VHS, OH, CL, MM, and VS reported no conflicts of interest. LH received lecture/consultant fees from MSD, Boston Scientific, INARI Medical and Johnson&Johnson, outside the submitted work. 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.

Data availability

All ICD and OPS codes used in this study are publicly available online. The data used in this study are aggregated results provided by the Federal Statistical Office of Germany (Statistisches Bundesamt, DEStatis), which were analysed on patient-level data at the RDC (source: RDC of the Federal Statistical Office and the Statistical Offices of the federal states, DRG Statistics 2005–2019, and own calculations).

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