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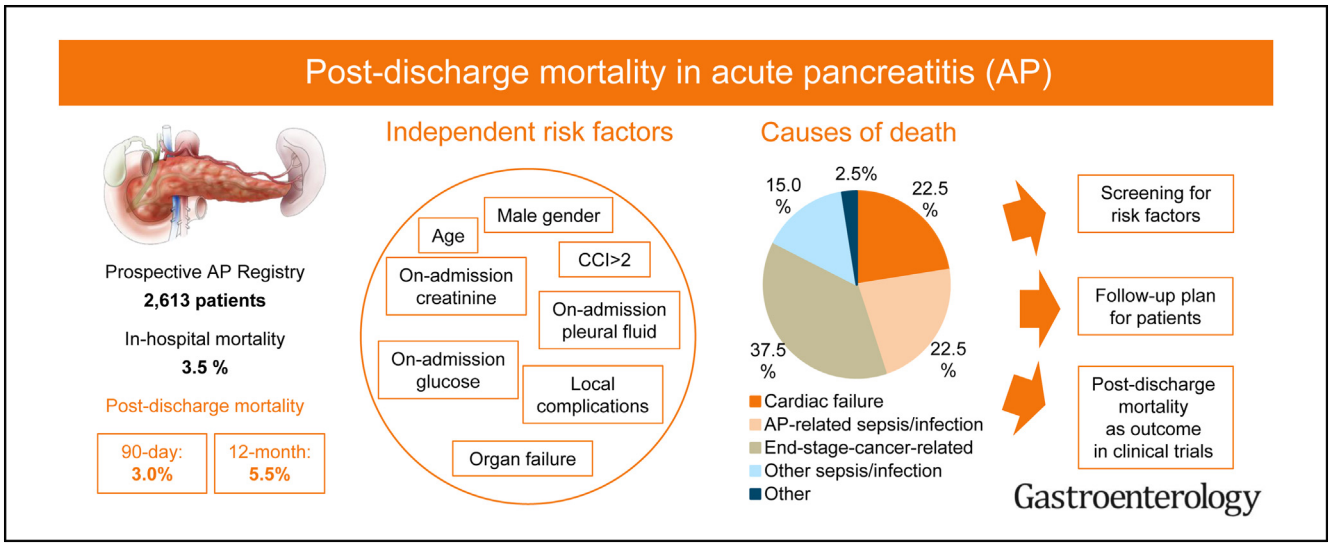
PANCREAS

Detailed Characteristics of Post-discharge Mortality in Acute Pancreatitis

Dóra Czapári,[1,2] Alex Váradi,[1,3,4] Nelli Farkas,[1,5] Gergely Nyári,[6] Katalin Márta,[2,7] Szilárd Váncsa,[1,2,7] Rita Nagy,[1,2,8] Brigitta Teutsch,[1,2] Stefania Bunduc,[2,7,9,10] Bálint Erőss,[1,2,7] László Czakó,[11] Áron Vincze,[12] Ferenc Izbéki,[13] Mária Papp,[14] Béla Merkely,[15] **Andrea Szentesi**,[1,*] and **Péter Hegyi**,[1,2,7,16,*] on behalf of the Hungarian Pancreatic Study Group

[1]Institute for Translational Medicine, Medical School, University of Pécs, Pécs, Hungary; [2]Center for Translational Medicine, Semmelweis University, Budapest, Hungary; [3]Department of Metagenomics, University of Debrecen, Debrecen, Hungary; [4]Department of Laboratory Medicine, University of Pécs, Pécs, Hungary; [5]Institute of Bioanalysis, Medical School, University of Pécs, Pécs, Hungary; [6]Department of Pathology, University of Szeged, Szeged, Hungary; [7]Institute of Pancreatic Diseases, Semmelweis University, Budapest, Hungary; [8]Heim Pál National Pediatric Institute, Budapest, Hungary; [9]Carol Davila University of Medicine and Pharmacy, Bucharest, Romania; [10]Fundeni Clinical Institute, Bucharest, Romania; [11]Department of Medicine, University of Szeged, Szeged, Hungary; [12]Department of Gastroenterology, First Department of Medicine, Medical School, University of Pécs, Pécs, Hungary; [13]Szent György Teaching Hospital of County Fejér, Székesfehérvár, Hungary; [14]Department of Gastroenterology, Institute of Internal Medicine, Faculty of Medicine, University of Debrecen, Debrecen, Hungary; [15]Heart and Vascular Center, Semmelweis University, Budapest, Hungary; and [16]Translational Pancreatology Research Group, Interdisciplinary Center of Excellence for Research Development and Innovation, University of Szeged, Szeged, Hungary



BACKGROUND & AIMS: The in-hospital survival of patients suffering from acute pancreatitis (AP) is 95% to 98%. However, there is growing evidence that patients discharged after AP may be at risk of serious morbidity and mortality. Here, we aimed to investigate the risk, causes, and predictors of the most severe consequence of the post-AP period: mortality. **METHODS:** A total of 2613 well-characterized patients from 25 centers were included and followed by the Hungarian Pancreatic Study Group between 2012 and 2021. A general and a hospital-based population was used as the control group. **RESULTS:** After an AP episode, patients have an approximately threefold higher incidence rate of mortality than the general population (0.0404 vs 0.0130 person-years). First-year mortality after discharge was almost double than in-hospital mortality (5.5% vs 3.5%), with 3.0% occurring in the first 90-day period. Age, comorbidities, and severity were the most significant independent risk factors for death following AP. Furthermore, multivariate analysis identified creatinine, glucose, and pleural fluid on admission as independent risk factors associated with post-discharge mortality. In the first 90-day period, cardiac failure and AP-related sepsis were among the main causes of death following discharge, and cancer-related cachexia and non–AP-related infection were the key causes in the later phase. **CONCLUSION:** Almost as many patients in our cohort died in the first 90-day period after discharge as during their hospital stay. Evaluation of cardiovascular status, follow-up of local complications, and cachexia-preventing oncological care should be an essential part of post-AP patient care. Future study protocols in AP must include at least a 90-day follow-up period after discharge.

Keywords: Post-discharge Mortality; Acute Pancreatitis; Cardiac Failure; Pseudocyst.

Acute pancreatitis (AP) is the most common gastrointestinal inflammatory disease that requires hospitalization.[1,2] Although 95% to 98% of patients survive the disease, it is still one of the leading causes of death among patients hospitalized with gastrointestinal disorders in the United States[3] and Europe.[4]

The severe form of AP is associated with high mortality during hospitalization.[1,2,5,6] It is therefore not surprising that research has mainly focused on preventing the development of severe AP and reducing in-hospital mortality. Our preliminary systematic search of randomized clinical trials (RCTs) in AP showed that mortality is the most frequent outcome. A total of 166 of the 217 RCTs used mortality as an outcome, but two-thirds of these articles only focused on in-hospital mortality (for details, see Supplementary Figure 1).

In contrast to considering mortality as an outcome in pancreas research, it has been shown that patients are at a higher risk of dying of numerous acute diseases after discharge than during hospitalization. For example, in severe acute hypertension, the in-hospital mortality was 7.9%, while it reached 29.4% at 12 months.[7] Long-term mortality after ST-segment-elevation myocardial infarction is higher than in-hospital mortality (7.0% vs 5.8% for women and 3.1% vs 2.5% for men, respectively).[8] These results suggest that the post-discharge period is at least as important as the hospitalization period with regard to the risk for mortality.

In this study, we aimed to investigate the risks, causes, and predictors of mortality of AP in the post-discharge period.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

The in-hospital survival of patients with acute pancreatitis is 95% to 98%. Information on post-discharge mortality is scarce. We investigated the risk, causes, and predictors of post–acute pancreatitis mortality in a well-characterized cohort of 2613 prospectively enrolled patients with acute pancreatitis.

NEW FINDINGS

Patients after acute pancreatitis have an approximately threefold higher incidence rate of mortality than the general population. Almost as many patients die in the first 90-day period after discharge as during hospital stay and due in substantial proportion to cardiac failure or sepsis.

LIMITATIONS

An etiology-based cohort would be much better as a control group, but a cohort of this size is not currently available.

CLINICAL RESEARCH RELEVANCE

Our results fundamentally change the management of patients with acute pancreatitis. A follow-up plan and screening program are crucially needed for patients with acute pancreatitis to reduce post-discharge complications and mortality. Post-discharge mortality should be an outcome parameter in acute pancreatitis–related clinical studies.

BASIC RESEARCH RELEVANCE

The currently available experimental models of acute pancreatitis are not suitable for investigating post–acute pancreatitis mortality. Preclinical animal models need to be developed to investigate the pathomechanism of sepsis and/or heart failure after acute pancreatitis.

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Methods

Preliminary Settings, Ethical Approval, and Patients' Consent

This study is a post hoc analysis of prospectively collected data from patients treated for AP following the STROBE guidelines for cohort studies. The Acute Pancreatitis Registry (APR) is maintained by the Hungarian Pancreatic Study Group (HPSG). The HPSG (https://tm-centre.org/en/study-groups/hungarian-pancreatic-study-group/) was established in 2011 to improve patient care for pancreatic diseases. The registry received ethical permission from the Scientific and Research Ethics Committee of the Medical Research Council (22254–1/2012/EKU, 17787–8/2020/EÜIG), and all the patients provided written informed consent to participate. The study protocol conforms to the Declaration of Helsinki ethical guidelines.[9]

Definitions

According to the International Association of Pancreatology/American Pancreatic Association and HPSG evidence-based guidelines,[10,11] AP is diagnosed when at least 2 of the following 3 criteria are met: (1) abdominal pain, (2) serum amylase or lipase elevation of at least 3 times the upper limit of normal, and (3) characteristic abnormalities seen on imaging. Severity and local and systemic complications were defined based on the modified Atlanta classification.[12]

Participants

Patients with AP from 27 centers have been enrolled in the registry since 2012. A total of 2944 patients consented to participate. Patients without information on post-discharge survival status were excluded. A total of 2613 patients from 25 centers were involved in the analyses, each of them with the earliest recorded AP episode. The cohort analyzed is representative of the total cohort (Supplementary Figure 2). Center

*** Authors share co-last authorship.**

Abbreviations used in this paper: **AP, acute pancreatitis; APR, Acute Pancreatitis Registry; CCI, Charlson Comorbidity Index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; DCoD, direct cause of death; eGFR, estimated glomerular filtration rate; HPSG, Hungarian Pancreatic Study Group; HR, hazard ratio; IR, incidence rate; IRR, incidence rate ratio; RCT, randomized clinical trial; UD, underlying disease.**

Most current article

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distribution is shown in Supplementary Table 1. The median follow-up time for patients was 3.1 years.

We used 2 control groups in our analysis. (1) For the general control group, we obtained data from the Hungarian Central Statistical Office to compare the mortality rates of patients with AP with those of the general population. Data on the number of annual births and deaths per age group between 2012 and 2019 were used for calculation. (2) For the hospital-based control group, we included data on gastroenterology patients who were treated in-hospital between 2018 and 2022 for reasons other than AP with no pancreas-related diseases in their histories.

Causes of death were investigated retrospectively based on autopsy and/or premortem clinical reports. We had information on causes of death for 220 of the 374 patients who died post-discharge. The analyzed population is representative of the total post-discharge mortality population of 374 patients (Supplementary Figure 3).

Data Collection

Anamnestic data on patients with AP and admission, examination, treatment, and AP outcome details were recorded in the APR. The sources of data were patient interviews and electronic and paper-based medical records. Data were collected by trained clinical research administrators, and a 4-checkpoint electronic clinical data management system was set up to ensure data quality. Further details on data collection and data quality for all the assessed variables are presented in Supplementary Table 2.

Outcomes and Causes of Death Analysis

In-hospital mortality was defined as cases when the death occurred during the index admission of AP. The fact and time of death were recorded in the APR for those who died during the in-patient period. Mortality after discharge was defined whenever the patient died post-discharge or during further hospital treatment for reasons other than AP. We requested data from the Personal Data and Address Register maintained by the Hungarian Ministry of the Interior for those who died during the follow-up period both in the AP and the hospital-based control populations. Hungarian legislation allows requests of patient-level data for scientific research.[13]

We also conducted an analysis on risks and causes of death focusing on the first 90-day post-discharge period. Two independent pathologists defined the underlying disease and the direct cause of death for all patients who died after discharge, and the information was available from the patient's medical documentation. Based on the available premortem clinical information and the autopsy reports, 2 categories of diseases were determined: underlying disease (UD) and direct cause of death (DCoD). The UD was determined based on Hungarian law (Government Decree 351/2013.[X. 4.] on postmortem examinations and the procedure for the dead, https://net.jogtar.hu/jogszabaly?docid=a1300351.kor), which regulates clinical treatment before death and from which determination of cause of death was developed.

We determined 4 main categories of UD: (1) cardiac (with a well-known primary or secondary cardiac disease from the clinical history or the autopsy report), (2) AP-related (with no other UD; AP defined according to the criteria provided earlier),[11] (3) cancer-related (defined by the pre- or postmortem histological confirmation of a malignant neoplasm), and (4) other (any other diseases except for the previously mentioned groups).

The DCoD was determined as cardiac failure if the acute signs of congestion could be detected and there were no signs of sepsis or neoplastic disorder. Death was considered as sepsis-related if clinical data confirmed a Sequential Organ Failure Assessment (SOFA) score or the Quick SOFA criteria reached or surpassed 2[14] and cancer-related if the UD was neoplastic and the clinical and postmortem examination showed metastatic procedure and none of the cardiac or septic causes were described. Any other DCoDs apart from those noted previously were labeled "other." When disagreement occurred, a third pathologist was involved (see Supplementary Figure 3 for representativity).

Statistical Analyses

We used descriptive statistical tools to characterize our data: mean and standard deviation (SD) were used for continuous variables. Frequencies and percentages were given for categorical variables. Chi-square or Fisher's exact test was used to compare the study cohort with the analyzed cohort for categorical variables, and the 2-sample Kolmogorov-Smirnov test was used for continuous parameters. The AP and hospital-based control groups were matched with optimal pair matching,[15] which minimizes the total distance across all pairs using the Charlson Comorbidity Index (CCI) categories (0, 1–2, 3–4, >5), age, gender, metastatic solid tumor, and moderate to severe liver disease covariates. However, the latter 3 variables were set to match exactly. To compare this matched dataset, we used the paired-samples Wilcoxon test for continuous data, McNemar's test for nominal variables, and random intercept logistic regression for categorical variables with multiple levels. We calculated the incidence rate (IR) and provided person-years (yearly number of mortality events per 1000 people) and incidence rate ratio (IRR) while comparing the mortality in the AP population and in the general population. Wilson 95% confidence intervals (CIs) for rates were calculated to compare mortality rates. Kaplan-Meier survival curves analysis with the log-rank test was used for univariate analysis of the relation between the observed parameters. Number at risk ranges were given in the categories used in the analyses. Cox proportional hazard regression analysis aided us in detecting independent influencing factors in the survival rate. For the analyses, continuous variables were transformed into categorical variables. We adjusted all multivariate models for age, gender, and comorbidities. We calculated hazard ratios (HR) with 95% CIs. We indicated HR and CI in the results section when 2 groups were analyzed. *P* values less than .05 were considered statistically significant.

All data handling and analyses occurred in the R (v4.03) statistical environment.[16] MatchIt (v4.5.2) was used to pair AP and control patients,[17] survival (v3.2–13)[18,19] was used for Cox regression models, survminer (v0.49) was used to visualize Kaplan-Meier curves,[20] and fmsb (v0.7.5) was used to estimate the IRR.[21] R packages were involved.

Results

Representativeness and General Characteristics of the Cohort

Age, gender, etiology, comorbidities, CCI, severity distribution, and in-hospital mortality were not different in the total (n = 2944) and analyzed (n = 2613) cohort

(Supplementary Figure 2). These data clearly show that the patient population in this study represents a general AP population. In our cohort of 2613 patients, 56.1% were male (n = 1466), and 43.9% were female (n = 1147). The average age was 57 ± 18 years. The most common AP etiologies were biliary (44.5%) and alcoholic (20.6%). The distribution of mild, moderately severe, and severe cases was 69.5%, 23.3%, and 7.2%, respectively. In-hospital mortality was 3.5% (n = 91), which was 0.3%, 2.3%, and 38.0% in the mild, moderately severe, and severe AP groups, respectively.

Mortality and General Survival in the Cohort

The 12-month post-discharge mortality rate was 5.5% for the total cohort, of whom 3.0% died in the first 90-day period. The IR of mortality in the total AP population was 0.0404 (40 person-years), and the IR was 0.0130 (13 person-years) in the general control population (the IRR for the AP population: 3.1; CI, 2.8–3.43; $P < .001$). The IR in the AP population (matched with the hospital-based control) was 0.050 (50 person-years) and 0.0697 (69 person-years) in the hospital-based control population, whereas the IRR for the matched AP population was 0.72; CI, 0.47–1.11, $P = .143$). AP is associated with a considerably increased mortality rate in the first 8 years after discharge compared with the general control population, whereas there is no difference for the hospital-based control group (Figure 1*A*, *B*, *D*, and *E*). In terms of the absolute number of deaths distribution, the early periods proved to be the most dangerous: 55.2% of the total 1-year mortality (143 deaths) occurred in the first 90-day period (Figure 1*C*), whereas 38.2% of the total 8-year mortality (374 deaths) took place in the first year (Figure 1*F*). Our analysis also showed that the higher mortality rates following AP are observed in all age groups between 20 and 90 years (Supplementary Figure 4). The survival curves confirm the mortality results and clearly demonstrate the crucial importance of the first 90 days after discharge (Figure 1*C* and *F*).

Twelve-Month Survival

Age and comorbidities are independent risk factors for shorter survival after discharge. *Univariate analysis.* We examined the links between anamnestic factors and 12-month survival (Figure 2). Age (HR, 1.05; CI, 1.04–1.06; $P < .001$), comorbidities (HR, 3.75; CI, 2.19–6.41; $P < .001$), the CCI ($P < .001$), and diabetes (HR, 1.53; CI, 1.06–2.21; $P = .023$) showed a significant indirect relation to the 12-month survival. No difference was found in survival by gender ($P = .307$), body mass index ($P = .291$), hypertension ($P = .362$), hyperlipidemia ($P = .087$), smoking ($P = .132$), or biliary ($P = .882$), alcohol-induced ($P = .202$), or idiopathic ($P = .418$) etiology. Hypertriglyceridemia-induced ($P = .021$) etiology and drinking ($P = .034$) were associated with longer survival. Further survival graphs are shown in Supplementary Figure 5, and statistical details can be found in Supplementary Table 2.

Multivariate analysis. Male gender (Female: HR, 0.59; CI, 0.36–0.97; $P = .036$), age (HR, 1.03; CI, 1.01–1.05; $P = .001$), and a CCI above 2 (CCI = 3: HR, 2.86; CI, 1.24–6.59; $P = .014$; CCI = 4: HR, 3.02; CI, 1.18–7.74; $P = .022$; CCI = 6: HR, 5.80; CI, 2.31–14.6; $P < .001$) were found to be independent risk factors for 12-month mortality (Supplementary Table 3).

On-admission creatinine, glucose levels, and pleural fluid are independent risk factors for shorter survival after discharge. *Univariate analysis.* Next, we investigated the relation between on-admission patient parameters and 12-month survival (Figure 3, Supplementary Figure 6). Higher blood urea nitrogen (HR between 2.08 and 5.02 in the 7.2–10.0 mmol/L and higher groups compared with the 3.6–7.2 mmol/L group; for details, see Supplementary Table 4), higher creatinine (HR between 1.59 and 3.46 in the 103–150 μmol/L and higher groups compared with the 55–103 μmol/L group), lower estimated glomerular filtration rate (eGFR 25–50 mmol/L: HR, 2.48; CI, 1.45–4.26; $P < .001$; eGFR <25 mmol/L: HR, 3.19; CI, 1.23–8.26; $P = .017$, compared with the eGFR >90 mmol/L group), higher admission C-reactive protein (CRP 50–150 mg/L: HR, 2.98; CI, 1.66–5.36; $P < .001$; CRP >150 mg/L: HR, 3.14; CI, 1.64–6.01; $P < .001$, compared with the CRP <5.2 mg/L group), lower hematocrit (HR, 2.14; CI, 1.37–3.35; $P < .001$ in the hematocrit <36% group compared with the 36%–48% group), and on-admission pleural fluid (HR, 1.77; CI, 1.01–3.11; $P = .047$) were risk factors for shorter survival. We found no link between amylase, lipase, HbA1c, triglyceride level, and 12-month survival. The statistical analysis results can be found in Supplementary Table 4.

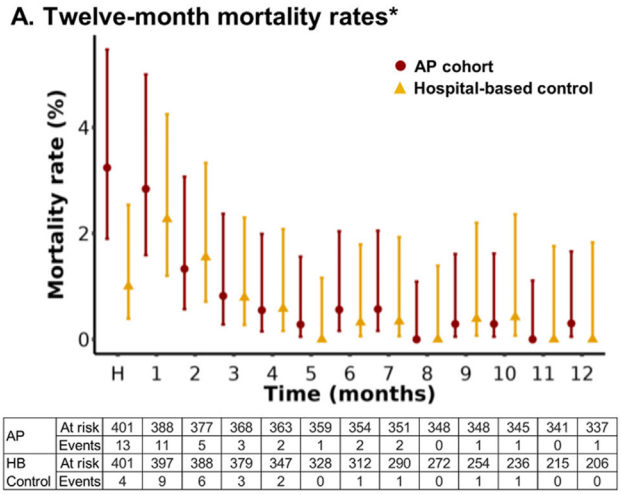
Multivariate analysis. In our multivariate analysis, on-admission creatinine (HR, 1.01; CI, 1.00–1.02; $P = .018$), glucose levels (HR, 1.18; CI, 1.07–1.29; $P < .001$), and pleural fluid (HR, 2.64; CI, 1.07–6.52; $P = .036$) were independent risk factors for 12-month survival (Supplementary Table 5).

Local complications and organ failure are independent risk factors for shorter survival after discharge. *Univariate analysis.* We also investigated the relation among severity, complications, length of hospital stay, and survival in the first 12-month period (Figure 4). Severe AP (HR, 3.78; CI, 2.28–6.29; $P < .0001$), hospital stay of longer than 22 days (HR, 3.24; CI, 1.96–5.35; $P < .001$), local complications (HR, 1.51; CI, 1.04–2.20; $P = .031$), necrosis (HR, 2.35; CI, 1.46–3.77; $P < .001$), and organ failure (HR, 3.44; CI, 2.22–5.33; $P < .001$) were associated with shorter survival. Statistical details can be found in Supplementary Table 6.

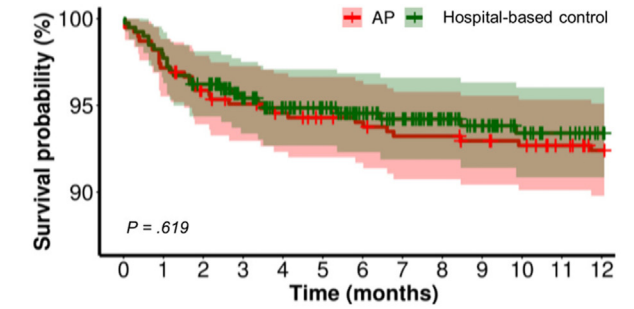
Multivariate analysis. In the multivariate analysis, we found that local complications (HR, 1.73; CI, 1.15–2.60; $P = .008$) and organ failure (HR, 1.89; CI, 1.16–3.07; $P = .010$) were found to be independent risk factors for shorter survival in the 12-month follow-up (Supplementary Table 7).

Eight-Year Survival

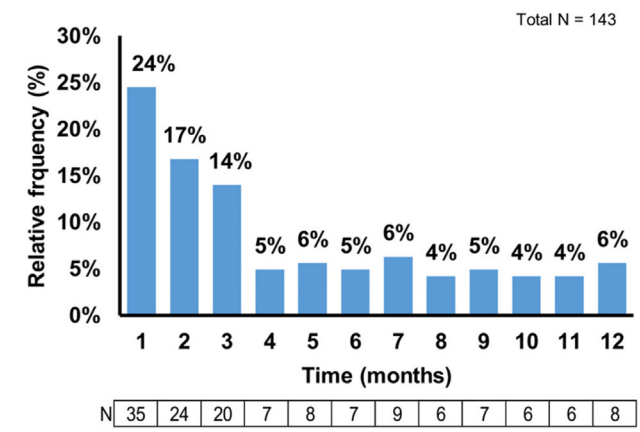
In multivariate models, male gender (Female: HR, 0.64; CI, 0.47–0.87; $P = .005$) age (HR, 1.04; CI, 1.03–1.06; $P < .001$), comorbidities, creatinine (HR, 1.01; CI, 1.00–1.02; $P = .001$), glucose level (HR, 1.14; CI, 1.06–1.22; $P < .001$), on-admission pleural fluid (HR, 2.17; CI, 1.11–4.24; $P = .023$), and organ failure (HR, 1.55; CI, 1.08–2.20; $P = .016$) during

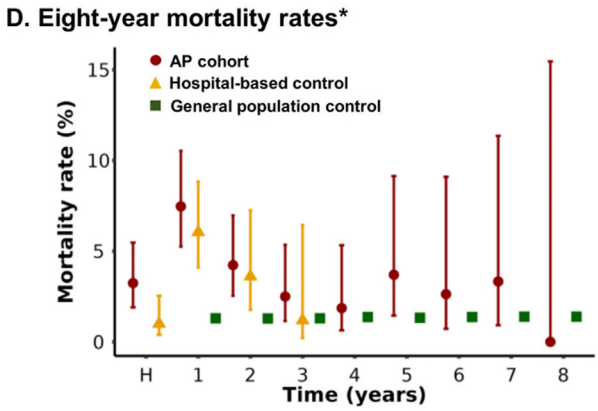


AP	At risk	401	388	377	368	363	359	354	351	348	348	345	341	337
	Events	13	11	5	3	2	1	2	2	0	1	1	0	1
HB Control	At risk	401	397	388	379	347	328	312	290	272	254	236	215	206
	Events	4	9	6	3	2	0	1	1	0	1	1	0	0

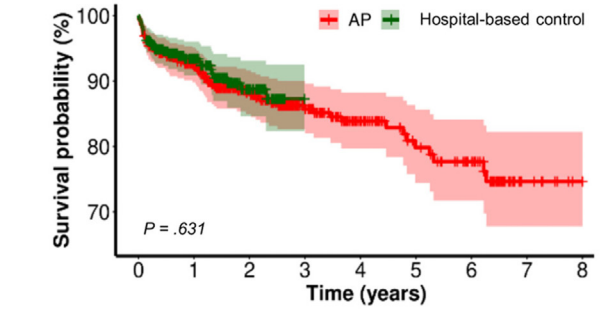


AP	At risk	388	377	368	363	359	354	352	348	348	345	342	337	331
	Events	0	11	5	3	2	1	1	3	0	1	1	0	1
HB Control	At risk	397	388	379	349	331	312	292	276	255	237	219	206	196
	Events	0	9	6	3	2	0	1	1	0	1	1	0	0





AP	At risk	401	388	331	240	161	108	76	60	21
	Events	13	29	14	6	3	4	2	2	0
HB Control	At risk	401	397	194	84					
	Events	4	24	7	1					
General Control	At risk		9931925	9802485	9676161	9550306	9553475	9554551	9423282	9292615
	Events		129440	126324	125855	131255	126615	131269	130667	129174



AP	At risk	388	331	240	161	108	76	60	21	13
	Events	0	29	14	6	3	4	2	2	0
HB Control	At risk	397	194	84	0	0	0	0	0	0
	Events	0	24	7	1	0	0	0	0	0

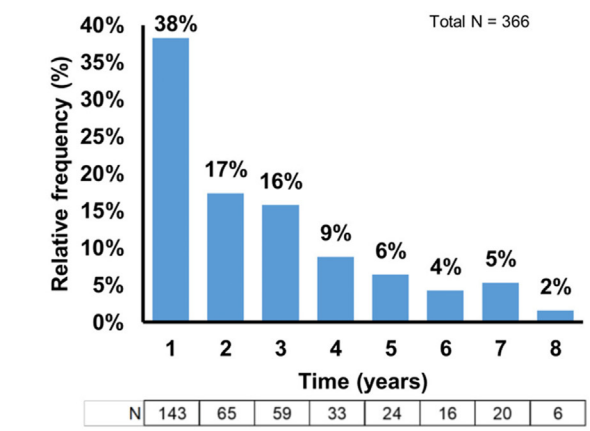


Figure 1. Mortality rates, survival, and mortality distribution in the post-AP period. (*A*) Twelve-month mortality rate of the matched AP and hospital-based control populations. (*B*) Twelve-month survival of the matched AP and hospital-based control populations. (*C*) Twelve-month mortality distribution of the total AP population. (*D*) Eight-year mortality rate of the general population and the matched AP and hospital-based control populations. (*E*) Eight-year survival of the matched AP and hospital-based control populations. (*F*) Eight-year mortality distribution of the total AP population. HB, hospital-based. *The AP cohort and the hospital-based control population are matched by sex, age, and comorbidities.

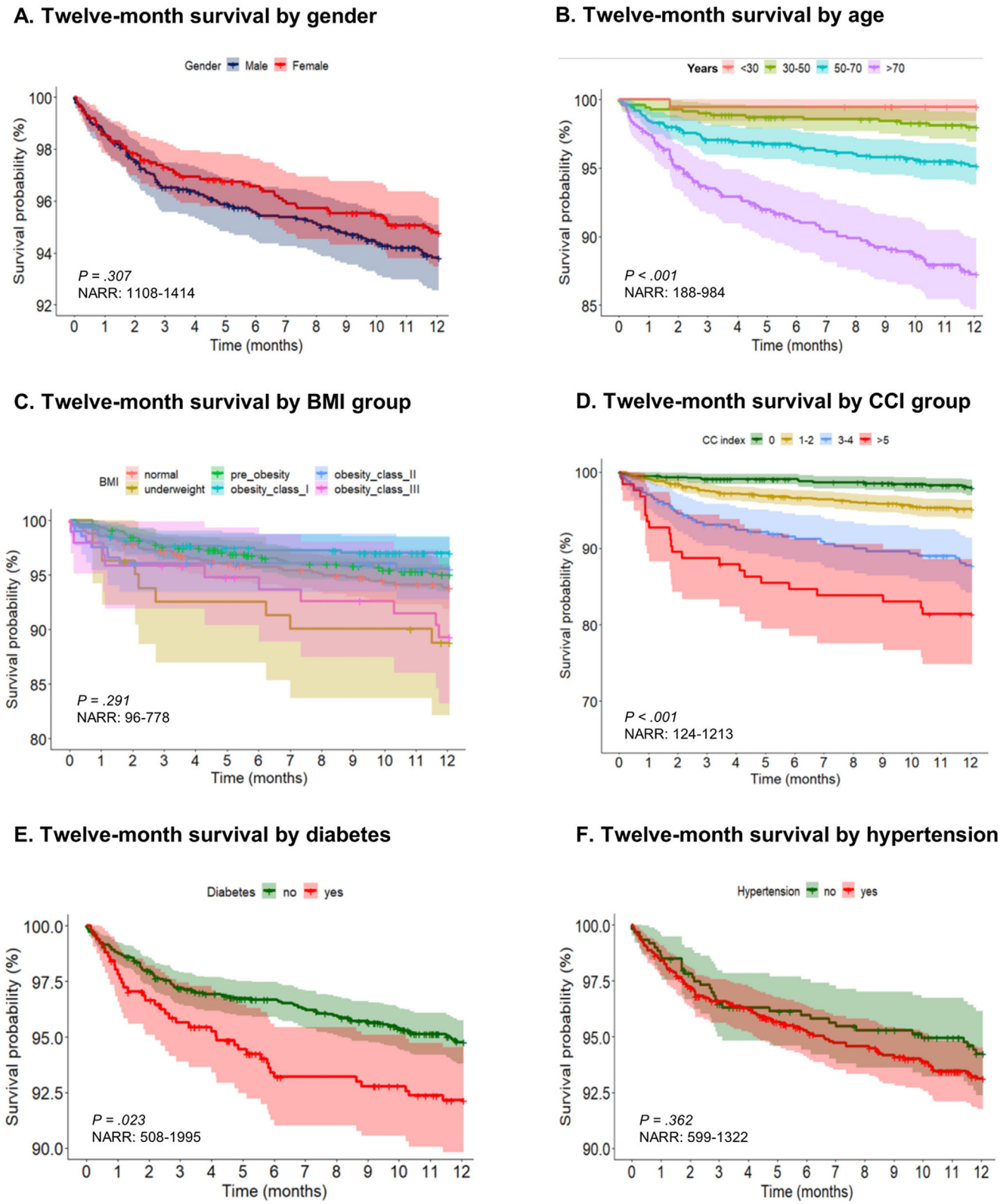


Figure 2. Twelve-month survival by anamnestic factor. (*A*) Gender. (*B*) Age. (*C*) BMI. (*D*) CCI. (*E*) Diabetes. (*F*) Hypertension. BMI, body mass index; NARR, "number at risk" range in groups at time of discharge. Details of the number at risk ranges can be found in Supplementary Table 2.

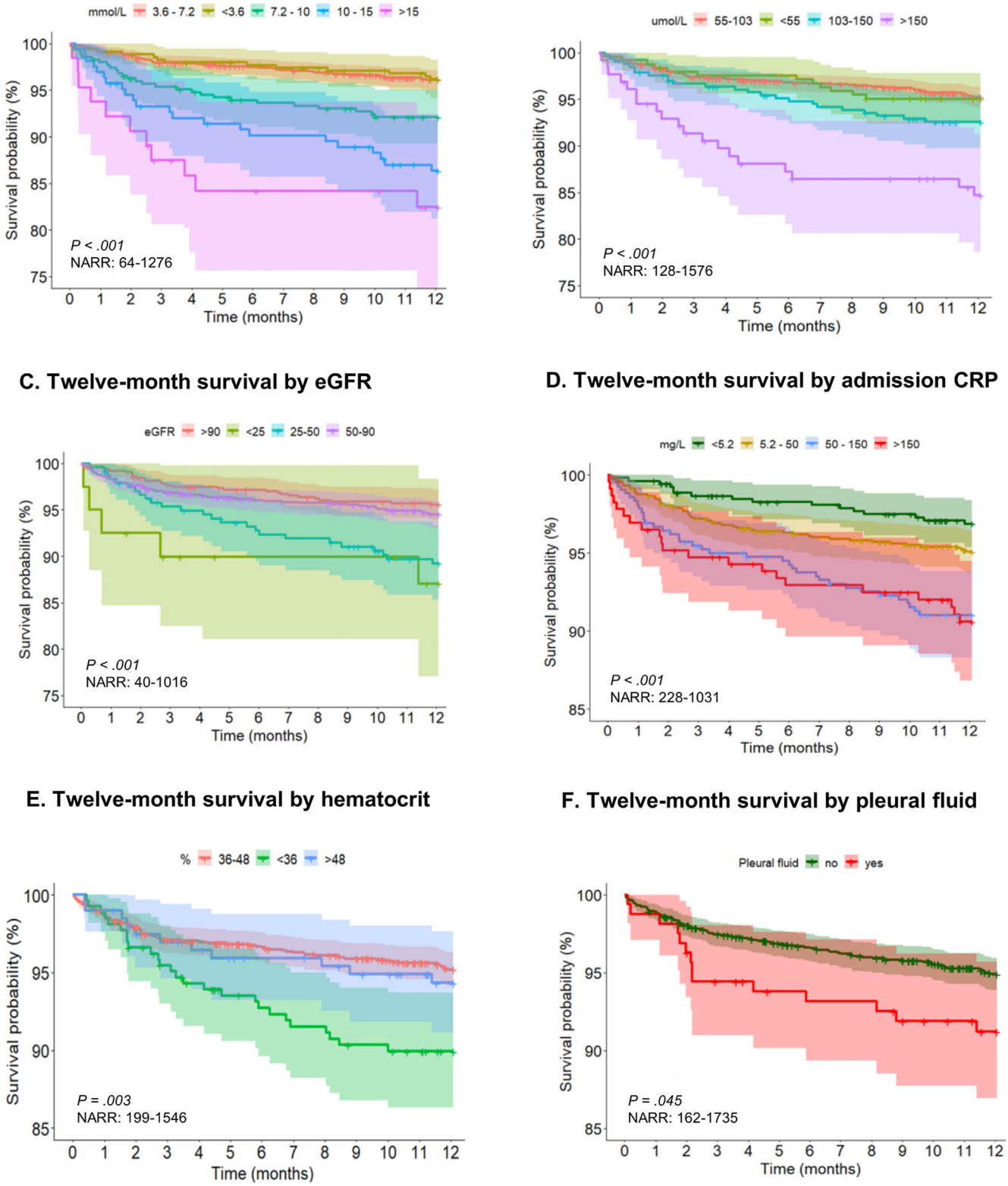


Figure 3. Twelve-month survival by admission parameter. (*A*) Blood urea nitrogen (mmol/L). (*B*) Creatinine (μmol/L). (*C*) eGFR. (*D*) Admission CRP. (*E*) Hematocrit. (*F*) Pleural fluid. BUN, blood urea nitrogen; NARR, "number at risk" range in groups at time of discharge. Details of the number at risk ranges can be found in Supplementary Table 4.

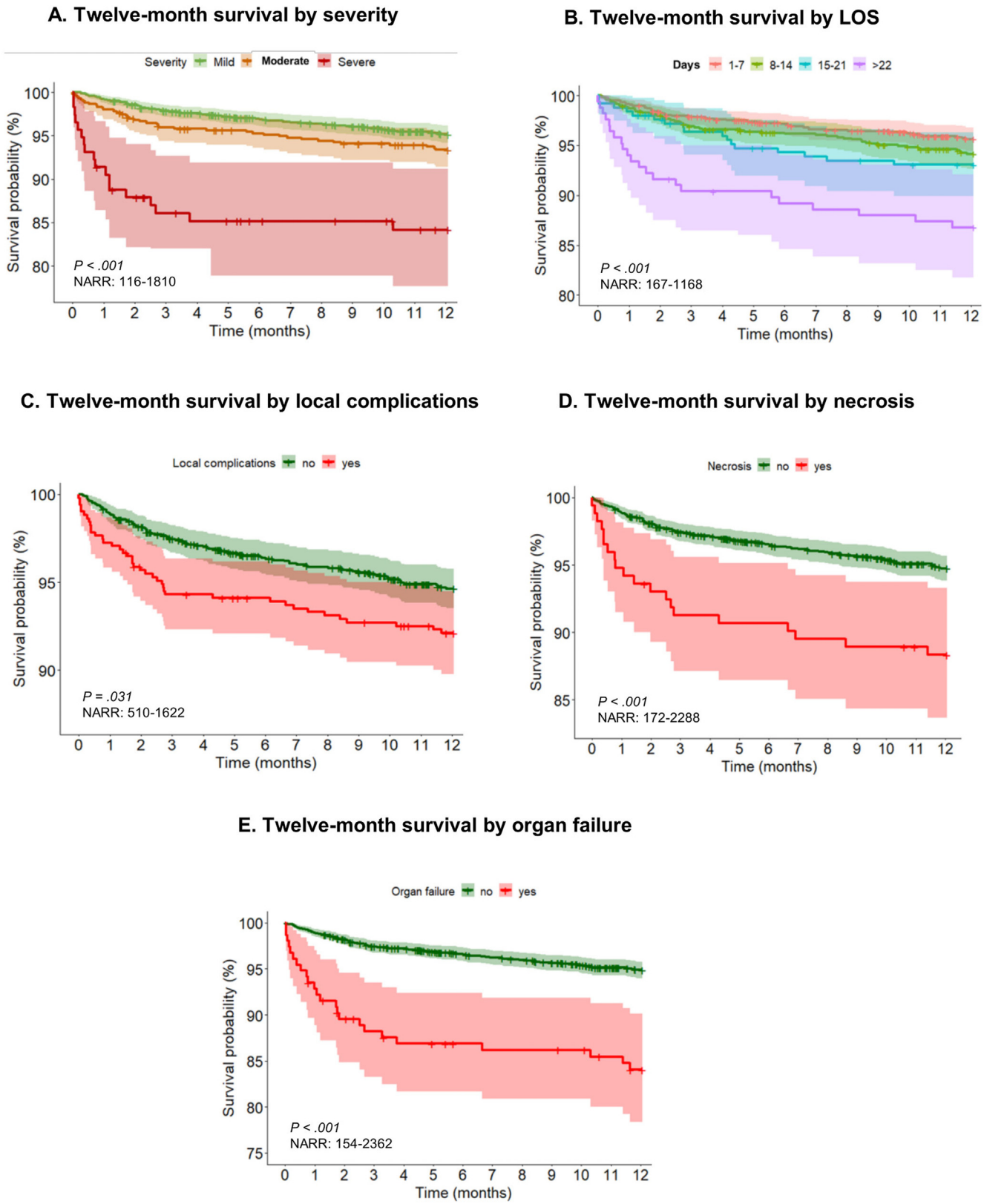


Figure 4. Twelve-month survival by AP outcome parameter. (*A*) Severity. (*B*) Length of hospital stay. (*C*) Local complications. (*D*) Necrosis. (*E*) Organ failure. LOS, length of hospital stay; NARR, "number at risk" range in groups at time of discharge. Details of the number at risk ranges can be found in Supplementary Table 6.

AP are independently associated with shorter survival in the 8-year survival analysis. A detailed 8-year survival analysis can be found in the Supplementary Material (Supplementary Figures 7–11).

Causes of Death

The first 90 days following discharge. According to our results described previously, the most critical period following discharge is the first 90 days. Therefore, we continued our post-discharge mortality analysis based on 3 periods: (1) the first 90 days, (2) 3–12 months following discharge, and (3) 1–8 years following discharge.

A total of 374 deaths (14.3% of the total cohort of 2613 patients) occurred after discharge within the 8-year follow-up period. Overall, 79 patients (21.1% of all post-discharge deaths) died in the first 90 days following discharge, a further 64 (17.1%) between 3 and 12 months, and 231 (61.8%) between 1 and 8 years. A total of 220 of 374 patients had detailed autopsy report, premortem clinical reports, or other medical documentation available. According to our representativity analysis, the characteristics (age, sex, severity, and length of hospital stay) of the 220 patients are representative of the total cohort of post-discharge deaths of 374 patients (Supplementary Figure 3).

There was a substantially higher proportion of severe and moderately severe disease course (severe: 20.3% vs 4.1%; moderately severe 30.4% vs 21.0%; $P < .001$) among the patients who died within 90 days, as shown in Figure 5*A*, as well as longer hospital stay (mean ± SD: 18 ± 22 vs 11 ± 8; $P = .007$). There was a difference in the CCI ($P = .037$) but not in gender, age, body mass index, and etiology between groups of patients who died within and over 90 days following discharge (Supplementary Table 11).

Causes of death in the post-AP period. In the first 90-day period, the leading causes of death were end-stage cancer (37.5%), cardiac failure (22.5%), AP-related sepsis (22.5%), and other non–AP-related sepsis, such as respiratory, pulmonary, or biliary infection (15.0%) (Figure 5*B*).

Between 3 and 12 months after discharge, end-stage cancer (43.2%), non–AP-related sepsis (20.5%), and cardiac failure (13.6%) were the leading causes of death.

In the period of 1 to 8 years, patients died of non–AP-related sepsis (45.6%) originating from respiratory, pulmonary, biliary, or urologic infections; end-stage cancer (27.9%); and cardiac failure (13.2%).

Causes of death by the major underlying diseases in the post-AP period. *First 90-day period.* We investigated the relationship between underlying diseases and direct causes of death in the first 90-day period. Patients with cardiac diseases died due to cardiac failure (12.5% of all patients who died within 90 days after discharge). Patients without other comorbidities died due to AP-related sepsis (22.5%) and cardiac failure (12.5%). Patients with cancer died of end-stage cancer (37.5%) and non–AP-related sepsis (5.0%) (Figure 5*C*).

Three- to 12-month period. Three to 12 months after discharge, patients with cardiac diseases died of cardiac failure (13.6%) and non–AP-related sepsis (6.8%), and patients with cancer died of end-stage cancer (43.2%) and non–AP-related sepsis (4.5%). Patients without other comorbidities died of AP-related infection (9.1%).

One- to 8-year period. Between 1 and 8 years, patients with cardiac diseases died of cardiac failure (13.2%) and non–AP-related sepsis (7.4%). On the other hand, patients with cancer died of end-stage cancer (27.9%) and non–AP-related sepsis (8.8%).

Patients with only AP and no other comorbidities. We had 19 patients who died after discharge without other comorbidities. Twelve of them died within 90 days following discharge, 3 of them of cardiac failure and 9 of them with pseudocysts of AP-related sepsis. Of the 9 patients with pseudocysts, there was an intervention in the case of 6 patients, with proof of infection in 5. Among the 5 patients who died 3 to 12 months following discharge, 1 had AP-related sepsis, 2 had recurrent AP, 1 had long treatment and multiple abdominal surgeries following a pseudocyst, and 1 had pulmonary embolism following a long hospitalization. Both patients who died more than 12 months after discharge had recurrent AP.

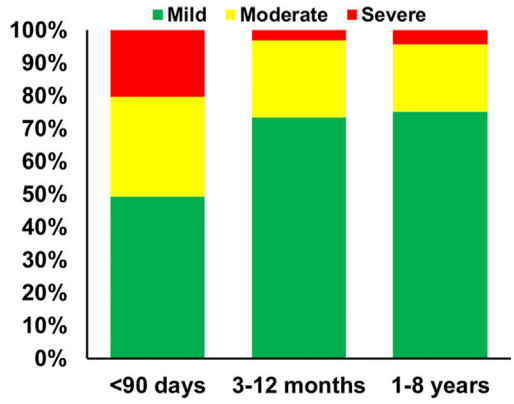
Discussion

In-hospital and Post-discharge Mortality

A large body of evidence is available on the factors that influence in-hospital mortality from our earlier analyses.[22–25] Physicians treating AP often consider it a great success when they can discharge their patients, although they have no evidence on the possible consequences of AP in the post-AP period. Our systematic review of 217 RCTs confirmed this and showed that only 32% of researchers investigated the post-AP period. This may cause a number of potential problems and biases. For example, (1) it could raise the possibility that very important, clinically relevant events are overlooked. On the other hand, (2) the low in-hospital mortality may discourage researchers from conducting important trials in AP. The latter raises further questions, since 75.3% of the RCTs have shown nonsignificant results in mortality, which could be due to either the underpowered analysis or an inappropriately chosen primary endpoint.

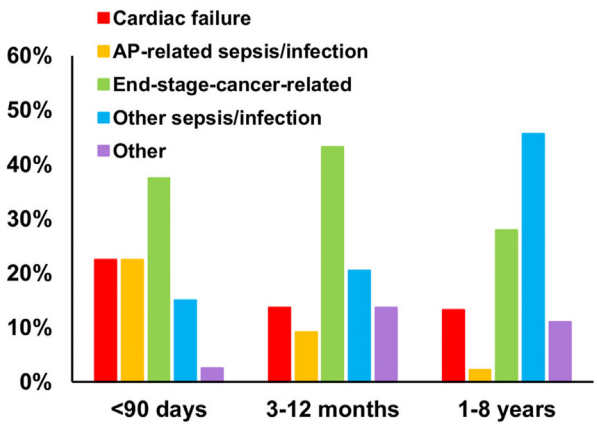
However, there is an increasing body of evidence on the importance of the post-discharge period in diseases affecting a larger population. For example, Coles et al[26] identified risk factors for post-discharge mortality among patients with acute myocardial infarction and emphasized the necessity of targeted surveillance and treatment. Mohr et al[27] investigated the relation between in-hospital and post-discharge mortality among patients hospitalized for sepsis and found that higher in-hospital mortality is linked to higher post-discharge mortality; the latter can therefore be decreased by improving in-patient and health care practices. The European Chronic Obstructive Pulmonary Disease (COPD) Audit identified risk factors associated with in-hospital and post-discharge mortality and concluded that improving acute COPD care by conducting blood gas measurements, spirometry, and noninvasive ventilation would improve COPD outcomes.[28] All these studies found that post-discharge mortality has considerable risk and could be

A. Severity



	N=79	N=64	N=231
(n; %)	16 (20.3%)	2 (3.1%)	10 (4.3%)
(n; %)	24 (30.4%)	15 (23.4%)	47 (20.3%)
(n; %)	39 (49.4%)	47 (73.4%)	174 (75.3%)

B. Direct causes of death



	N=40	N=44	N=136
(n; %)	9 (22.5%)	6 (13.6%)	18 (13.2%)
(n; %)	9 (22.5%)	4 (9.1%)	3 (2.2%)
(n; %)	15 (37.5%)	19 (43.2%)	38 (27.9%)
(n; %)	6 (15.0%)	9 (20.5%)	62 (45.6%)
(n; %)	1 (2.5%)	6 (13.6%)	15 (11.0%)

C. Underlying diseases

UNDERLYING DISEASE	DIRECT CAUSE OF DEATH: CARDIAC FAILURE	AP-RELATED SEPSIS/INFECTION	CANCER-RELATED	OTHER SEPSIS/INFECTION	OTHER
CARDIAC 6 CASES	12.5%			2.5%	
ACUTE PANCREATITIS* 12 CASES	7.5%	22.5%			
CANCER 17 CASES			37.5%	5.0%	
OTHER COMORBIDITIES 5 CASES	2.5%			7.5%	2.5%

<90 days

% of patients who died within 90 days after discharge (N=40)
*No other comorbidities

UNDERLYING DISEASE	DIRECT CAUSE OF DEATH: CARDIAC FAILURE	AP-RELATED SEPSIS/INFECTION	CANCER-RELATED	OTHER SEPSIS/INFECTION	OTHER
CARDIAC 9 CASES	13.6%			6.8%	
ACUTE PANCREATITIS* 5 CASES		9.1%			2.3%
CANCER 23 CASES			43.2%	4.5%	4.5%
OTHER COMORBIDITIES 7 CASES				9.1%	6.8%

3-12 months

% of patients who died 3-12 months after discharge (N=44)
*No other comorbidities

UNDERLYING DISEASE	DIRECT CAUSE OF DEATH: CARDIAC FAILURE	AP-RELATED SEPSIS/INFECTION	CANCER-RELATED	OTHER SEPSIS/INFECTION	OTHER
CARDIAC 28 CASES	13.2%			7.4%	
ACUTE PANCREATITIS* 2 CASES		0.7%		0.7%	
CANCER 52 CASES			27.9%	8.8%	1.5%
OTHER 54 CASES		1.5%		28.7%	9.6%

1-8 years

% of patients who died 1-8 years after discharge (N=136)
*No other comorbidities

Figure 5. Severity, direct causes of death, and underlying diseases. (*A*) Severity. (*B*) Direct causes of death. (*C*) Underlying diseases.

decreased with different patient management, treatment, or surveillance measures.

In this study, we followed up an unprecedentedly high number of patients with AP and investigated the causes of death. In our cohort, the general in-hospital mortality rate was 3.5%, and it was 38% in the severe AP group. It is essential to state that our patient cohort is comparable with other AP cohorts worldwide.[29–31] In our analysis, we found that the mortality rate in the first 90 days after discharge almost reaches the in-hospital mortality rate (3.0% vs 3.5%), whereas the 1-year post-discharge mortality is 5.4%, which is consistent with earlier published retrospective data.[32]

Independent Risk Factors of Post-discharge Mortality

According to our findings, age, comorbidities, creatinine, glucose, pleural fluid on admission, local complications, and organ failure were independent risk factors for shorter survival after discharge. Unfortunately, very few data on post-discharge mortality risk factors in AP is available. However, Lee et al[32] identified 30-day readmission, higher CCI, and longer hospital stay as risk factors for 1-year post-discharge mortality in AP.

Consistent with our results, severity is an important prognostic factor for post-discharge prognosis in patients with cardiac failure,[33] community-acquired pneumonia,[34] and sepsis.[35] Further, the severity of sepsis and organ dysfunction in the acute phase is associated with long-term mortality, according to Shankar-Hari et al.[36]

Causes of Death Following Discharge

Cardiac failure was one of the leading causes of death after discharge. Patients with cardiac diseases also have more severe disease courses in other diseases. COVID-19 survivors with cardiovascular comorbidities have a higher risk for post-discharge mortality.[37] As in other acute diseases, cardiac complications during AP may cause myocardial injury and heart failure.[38] Nøjgaard et al[39] found that cardiac and gastrointestinal diseases and malignancies were the most common causes of long-term death following AP.

In our cohort, the second most frequent cause of post-discharge mortality was AP-related sepsis in the first year. The main risk factor for AP-related sepsis was pseudocyst formation. According to our earlier analysis, most newly formed pseudocysts occur within 2 weeks of hospital admission and are associated with more severe disease and longer hospitalization.[24] Pseudocysts may resolve without intervention but may also require special attention. The post-discharge mortality of 8 of the 18 patients without other comorbidities was pseudocyst-related in our cohort, thus emphasizing the utmost importance of discharge surveillance of pseudocysts and follow-up.

In the present cohort, patients with cancer as a comorbidity died of cancer-related cachexia and non–AP-related sepsis or infection. In recent decades, the definition of cancer-related cachexia has evolved from being a nutritional syndrome to a more complex one. The importance of systemic inflammation has been recognized, together with its metabolic consequences.[40] Nutrition and inflammation with metabolic aspects play an essential role in AP.

In addition, AP may be an early sign of pancreatic cancer.[41] Moreover, symptoms such as dilation of the main pancreatic duct, vascular invasion, and anemia elevate the risk of tumor etiology.[42] As cancer-related cachexia develops in a few months, it is crucial to identify the tumor as the etiology of AP.

It is extremely important to identify risk factors and develop follow-up plans for patients with AP. Patients treated in rehabilitation centers after sepsis or septic shock showed significantly better 5-year survival.[43]

Strengths and Limitations

To the best of our knowledge, this is the first comprehensive analysis of mortality following discharge in patients admitted with AP. We used an extensive database and long-term follow-up. We also investigated the relation between the underlying comorbidities and direct causes of death involving information from autopsy reports. The study has some limitations as well. The general population is not ideal as a control. We used a hospital-based control population as well, which is closer to the optimal; however, there are still differences between this and the AP population. An etiology-based cohort would be ideal. However, a cohort of this size is not currently available, and it is not feasible to build it for this analysis. The median follow-up time was 3.1 years, as patients who were enrolled in our prospective patient registry toward the end of the inclusion period will not have a full 8-year follow-up. We should therefore interpret the 8-year survival investigation with limitations. In the survival analyses, we transformed continuous variables into categorical variables, which may cause loss of information. The data on the causes of death were retrospective; a well-designed, prospective clinical trial would thus increase the level of evidence. Finally, the health care system may be different in each country. One should thus consider local circumstances in evaluating the implications of our results. Although the general performance of the Hungarian health care system is behind that of some countries in Western Europe, patient care for AP and some other diseases (eg, in cardiology) is comparable to that in other countries with generally better health care (Supplementary Material, p. 44).

Implications for Practice and Research

Our results show that patients with cardiac diseases, severe disease course, or pseudocysts need closer surveillance in the in-patient period and following discharge. A follow-up plan is recommended for patients with AP to reduce post-discharge complications and mortality.

Further research is needed to investigate the reasons for cardiac failure and sepsis leading to mortality in the first 3 months after discharge.

When planning clinical trials, it is essential to include post-discharge mortality as an outcome. Moreover, it is recommended that previous clinical trials be retrospectively reevaluated with this outcome parameter.

Conclusion

Almost as many patients die in the first 3 months after discharge as during their hospital stay. It is therefore

essential to revise follow-up practices in AP, especially for those with severe AP, cardiac diseases, and pseudocyst.

Our results fundamentally redefine the critical outcome indicators for AP and suggest that previous clinical trials should be reassessed for post-discharge mortality and that current trial protocols should include patient follow-up for at least 3 months after discharge.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2023.05.028.

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Correspondence
Address correspondence to: Péter Hegyi, MD, PhD, DSc, MAE, Institute of Pancreatic Diseases, Semmelweis University, H-1083 Budapest, Tömő u. 25-29, Hungary. e-mail: hegyi2009@gmail.com.

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The Hungarian Pancreatic Study Group includes Péter Jenő Hegyi,[1,2] Andrea Párniczky,[1,3,4] Mária Földi,[4,5] Klementina Ocskay,[1,3] Márk Félix Juhász,[1,4] Marcell Imrei,[1,3,4] Szabolcs Kiss,[4,5] Alexandra Mikó,[1,6] Szilárd Gódi,[7] Judit Bajor,[7] Roland Hágendorn,[7] Patrícia Sarlós,[7] Imre Szabó,[7] József Czimmer,[7] Nándor Faluhelyi,[8] Péter Kanizsai,[9] Attila Miseta,[10] Tamás Nagy,[10] László Gajdán,[11] Adrienn Halász,[11] Balázs Németh,[12] Balázs Kui,[12] Dóra Illés,[12] Tamás Takács,[12] László Tiszlavicz,[13] Orsolya Oláh-Németh,[13] Bence Radics,[13] Zsuzsanna Vitális,[14] József Hamvas,[15] Márta Varga,[16] Barnabás Bod,[17] János Novák,[18] Pál Maurovich-Horváth,[19] Attila Doros,[20] Pál Ákos Deák,[21] Csaba Varga,[22] Szabolcs Gaál,[22] László Zubek,[23] János Gál,[23] Zsolt Molnár,[23] Tamás Tornai,[2] Balázs Lázár,[2] Tamás Hussein,[2] Bea Kovács,[2] Anna Németh,[2] Dorottya Tarján,[2] Mónika Lipp,[2] Orsolya Urbán,[2] Simon Tóth,[2] Dániel Söti,[3,24] and Dávid Becker[25]; from the [1]Institute for Translational Medicine, Medical School, University of Pécs, Pécs, Hungary; [2]Institute of Pancreatic Diseases, Semmelweis University, Budapest, Hungary; [3]Center for Translational Medicine, Semmelweis University, Budapest, Hungary; [4]Heim Pál National Pediatric Institute, Budapest, Hungary; [5]Doctoral School of Clinical Medicine, University of Szeged, Szeged, Hungary; [6]Department of Medical Genetics, Medical School, University of Pécs, Pécs, Hungary; [7]Department of Gastroenterology, First Department of Medicine, Medical School, University of Pécs, Pécs, Hungary; [8]Department of Medical Imaging, Medical School, University of Pécs, Pécs, Hungary; [9]Department of Emergency Medicine, Medical School, University of Pécs, Pécs, Hungary; [10]Department of Laboratory Medicine, Medical School, University of Pécs, Pécs, Hungary; [11]Szent György Teaching Hospital of County Fejér, Székesfehérvár, Hungary; [12]Department of Medicine, University of Szeged, Szeged, Hungary; [13]Department of Pathology, University of Szeged, Szeged, Hungary; [14]Department of Gastroenterology, Institute of Internal Medicine, Faculty of Medicine, University of Debrecen, Debrecen, Hungary; [15]Peterfy Hospital, Budapest, Hungary; [16]Department of Gastroenterology, BMKK Dr. Rethy Pál Hospital, Békéscsaba, Hungary; [17]Dr. Bugyi István Hospital, Szentes, Hungary; [18]Pándy Kálmán Hospital of Békés County, Gyula, Hungary; [19]Department of Radiology, Medical Imaging Center, Semmelweis University, Budapest, Hungary; [20]Department of Interventional Radiology, Heart and Vascular Center, Semmelweis University, Budapest, Hungary; [21]Division of Oncological Intervention, Department of Interventional Radiology, Heart and Vascular Center, Semmelweis University, Budapest, Hungary; [22]Department of Emergency Medicine, Semmelweis University, Budapest, Hungary; [23]Department of Anesthesiology and Intensive Therapy, Semmelweis University, Budapest, Hungary; [24]Medical School, Semmelweis University, Budapest, Hungary; and [25]Heart and Vascular Center, Semmelweis University, Budapest, Hungary.

CRediT Authorship Contributions
Dóra Czapári, LLM (Data curation: Lead; Formal analysis: Equal; Investigation: Equal; Project administration: Lead; Writing – original draft: Equal; Writing – review & editing: Equal).
Alex Váradi, MSc (Formal analysis: Equal; Methodology: Equal; Visualization: Equal; Writing – review & editing: Supporting).
Nelli Farkas, PhD (Formal analysis: Equal; Methodology: Equal; Writing – review & editing: Supporting).
Gergely Nyári, MD (Data curation: Equal; Formal analysis: Supporting; Writing – review & editing: Supporting).
Katalin Márta, PhD (Data curation: Equal; Methodology: Supporting; Writing – review & editing: Supporting).
Szilárd Váncsa, MD (Data curation: Equal; Writing – review & editing: Supporting).
Rita Nagy, MD (Data curation: Equal; Project administration: Supporting; Writing – review & editing: Supporting).
Brigitta Teutsch, MD (Data curation: Equal; Methodology: Supporting; Writing – review & editing: Supporting).
Stefania Bunduc, MD (Data curation: Equal; Methodology: Supporting; Writing – review & editing: Equal).
Bálint Erőss, PhD (Data curation: Equal; Methodology: Supporting; Resources: Equal; Writing – review & editing: Equal).
László Czakó, DSc (Data curation: Equal; Resources: Equal; Writing – review & editing: Equal).
Áron Vincze, PhD (Data curation: Equal; Resources: Equal; Writing – review & editing: Equal).
Ferenc Izbéki, DSc (Data curation: Equal; Resources: Equal; Writing – review & editing: Equal).
Mária Papp, DSc (Data curation: Equal; Resources: Equal; Writing – review & editing: Supporting).
Béla Merkely, DSc (Investigation: Equal; Writing – review & editing: Equal).
Andrea Szentesi, PhD (Data curation: Lead; Formal analysis: Equal; Funding acquisition: Equal; Visualization: Equal; Writing – original draft: Lead).
Péter Hegyi, DSc (Conceptualization: Lead; Funding acquisition: Lead; Investigation: Lead; Methodology: Lead; Resources: Lead; Writing – original draft: Lead).

Conflicts of interest
The authors disclose no conflicts.

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Data Availability
Original raw data are available from the corresponding author on reasonable request.