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ORIGINAL RESEARCH ARTICLE

Effect of precipitating factors of acute heart failure on readmission and long-term mortality

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Abstract

Aims Acute heart failure (AHF) is one of the leading causes of unscheduled hospitalization and is associated with frequent readmissions and substantial mortality. Precipitating factors of AHF influence short-term mortality, but their effect on outcome after hospital discharge is unknown. The present study assessed the effect of precipitating factors on readmission and long-term survival in the overall population and in patients aged 75 years or younger.

Methods and results Patients admitted with AHF ($n = 755$) included in the multicentre cohort 'Biomarcoeurs' were included in the study. Precipitating factors of AHF were classified in four main groups: acute coronary syndrome, atrial fibrillation, acute pulmonary disease and other causes. Hospital readmission during 90 days after discharge and survival at 1 year were analysed. Precipitating factors influenced readmissions and survival. Acute pulmonary disease was associated with fewer readmissions (HR 0.61, 95% confidence interval (CI) 0.37–0.99, $P = 0.049$), especially in patients aged 75 years or younger (HR 0.20, 95% CI 0.06–0.63, $P = 0.006$), whereas atrial fibrillation (HR 2.23, 95% CI 1.29–3.85, $P = 0.004$) and acute coronary syndrome (HR 2.23, 95% CI 1.02–4.86, $P = 0.044$) were associated with more readmissions. Patients with acute pulmonary disease at admission showed higher mortality (HR 1.59, 95% CI 1.04–2.43, $P = 0.034$), especially in subjects aged 75 years or younger (HR 2.52, 95% CI 1.17–5.41, $P = 0.018$).

Conclusions Precipitating factors of AHF substantially influenced outcome after hospitalization. In particular, patients with AHF precipitated by acute pulmonary disease showed fewer readmissions and higher 1 year mortality, especially in patients aged 75 years or younger.

Keywords Acute heart failure; Precipitating factor; Pulmonary disease; Readmission; Mortality

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Introduction

Acute heart failure (AHF) is one of the leading causes of unscheduled hospitalization in patients older than 65 years and is associated with frequent readmissions and substantial mortality.[1] In recent years, several factors that may contribute to exacerbation of heart failure have been identified. Among these, acute coronary syndrome, arrhythmias and acute respiratory disease have been identified as being the most common precipitating factors.[2–5] As shown in the analysis of the OPTIMIZE-HF registry, which included patients admitted for AHF in 259 centres in the United States, precipitating factors of AHF influenced short-term outcome.[2] In particular, acute coronary syndrome and acute respiratory disease were associated with higher in-hospital mortality. In contrast, little evidence is available about the effect of precipitating factors on readmission and long-term mortality.

We recently showed that the effect on outcome of several prognostic factors was strongly influenced by age and was more pronounced in AHF patients younger than 75 years, compared with the older ones.[6] The aim of the present study was to assess the effect of precipitating factors of AHF on

Table 1 Baseline characteristics at admission of patients with AHF

Clinical characteristics		All patients (n = 755)	Precipitating factor		*P-value*
			No acute pulmonary disease (n = 149)	Acute pulmonary disease (n = 606)	
Demographics	Age (years)	75 (64–84)	78 (66–88)	73 (64–82)	0.001
	Male gender	425 (56%)	73 (49%)	352 (58%)	0.053
Clinical signs	SBP (mmHg)	140 (120–162)	140 (114–161)	140 (120–162)	0.613
	DBP (mmHg)	80 (68–93)	75 (65–90)	80 (70–94)	0.007
	Heart rate (per min)	88 (72–105)	90 (76–112)	87 (72–105)	0.067
	Respiratory rate (per min)	26 (22–32)	29 (24–34)	26 (22–32)	< 0.001
	Oxygen saturation (%)	95 (90–97)	93 (88–96)	95 (91–97)	< 0.001
	Rales	582 (82%)	118 (87%)	464 (81%)	0.081
	Wheezing	144 (19%)	65 (44%)	79 (13%)	< 0.001
	Jugular distension	310 (41%)	54 (36%)	256 (42%)	0.194
	Peripheral edema	431 (57%)	77 (52%)	354 (58%)	0.140
	Temperature (°C)	36.9 (36.5–37.2)	37 (36.5–37.5)	36.8 (36.5–37.1)	< 0.001
	Height (cm)	168 (160–173)	167 (159–171)	168 (160–173)	0.058
	Weight (kg)	73 (63–85)	75 (62–88)	72 (63–85)	0.880
Comorbidities					
	Chronic heart failure	358 (47%)	67 (45%)	291 (48%)	0.523
	Coronary artery disease	246 (33%)	55 (37%)	191 (32%)	0.207
	Prior PCI/CABG	93 (12%)	18 (12%)	75 (12%)	1.000
	Peripheral vascular disease	78 (10%)	14 (9.4%)	64 (11%)	0.765
	Valve disease	97 (13%)	15 (10%)	82 (14%)	0.278
	Atrial fibrillation or flutter	286 (38%)	61 (41%)	225 (37%)	0.398
	Hypertension	520 (69%)	103 (69%)	417 (69%)	1.000
	Diabetes mellitus	274 (36%)	51 (34%)	223 (37%)	0.570
	Dyslipidemia	205 (27%)	34 (23%)	171 (28%)	0.217
	Obesity	78 (10%)	16 (11%)	62 (10%)	0.881
	Active or recent smoking	137 (18%)	31 (21%)	106 (18%)	0.344
	COPD or asthma	132 (18%)	62 (42%)	70 (12%)	< 0.001
	Chronic kidney disease	106 (14%)	21 (14%)	85 (14%)	1.000
	Depression	28 (3.7%)	8 (5.4%)	20 (3.3%)	0.230
	Cognitive dysfunction	39 (5.2%)	8 (5.4%)	31 (5.1%)	0.838
	Loss of autonomy	21 (2.8%)	11 (7.4%)	10 (1.7%)	0.001
	Chronic liver disease	13 (1.7%)	4 (2.7%)	9 (1.5%)	0.299
	Active or recent cancer	70 (9.3%)	13 (8.7%)	57 (9.4%)	0.876
	Anaemia	37 (4.9%)	8 (5.4%)	29 (4.8%)	0.832
Chronic treatment	Betablockers	310 (41%)	61 (41%)	249 (41%)	1.000
	ACE-I or ARB	417 (55%)	77 (52%)	340 (56%)	0.358
	MRA	104 (14%)	16 (11%)	88 (14%)	0.288
	Diuretics	433 (57%)	90 (60%)	343 (57%)	0.407
	Antiplatelets	304 (40%)	67 (45%)	237 (39%)	0.193
Biology	BNP (pg/mL)	1082 (611–2190)	899 (404–1445)	1191 (643–2329)	<0.001
	Troponin I (μg/L)	0.05 (0.02–0.129)	0.05 (0.02–0.2)	0.05 (0.02–0.12)	0.403
	Troponin T (μg/L)	0.02 (0.01–0.11)	0.04 (0.01–0.2)	0.01 (0.01–0.11)	0.787
	Creatinine (μmol/L)	108 (78–146)	106 (79–146)	108 (78–146)	0.838
	eGFR (Cockroft)	51.5 (34.9–75)	49.3 (32.4–69.2)	51.6 (35–75)	0.614
	CRP (mg/L)	16 (6–42)	35 (10–110)	14 (5–31)	< 0.001
	Procalcitonin (μg/L)	0.12 (0.08–0.22)	0.16 (0.12–0.36)	0.11 (0.08–0.16)	0.013

ACE-I, angiotensin converting enzyme inhibitor; AHF, acute heart failure; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CRP, c-reactive protein; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; MRA, mineralocorticoid receptor antagonist; PCI, percutaneous coronary intervention; SBP, systolic blood pressure.

readmission and long-term mortality in the overall population of patients admitted for AHF and in the subgroup of patients aged 75 years or younger.

Methods

Study population and diagnosis groups

Patients with diagnosis of AHF included in the multicentric prospective cohort 'Biomarcoeurs' were analysed in this study. The 'Biomarcoeur' cohort included patients aged 18 years or older admitted to the emergency department of three tertiary centres (Lariboisière University Hospital in Paris, France, Fattouma Bourguiba University Hospital in Monastir, Tunisia, and Cumhuriyet University Hospital in Sivas, Turkey) between 1 January 2010 and 31 December 2013. AHF (including *de novo* AHF, acute decompensated heart failure or cardiogenic shock) was diagnosed by reviewing medical records after hospital discharge and was based on medical history, clinical examination, natriuretic peptides and additional tests obtained during

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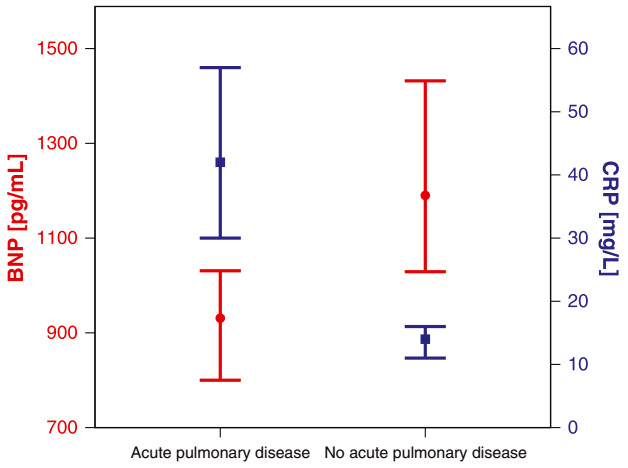
Figure 1 Levels of BNP and CRP (C-reactive protein) at admission in the group of patients with acute heart failure precipitated by acute pulmonary disease ($n = 149$) compared with acute heart failure precipitated by non-pulmonary causes ($n = 606$). Median and 95% confidence interval are displayed.



hospitalization. Precipitating factors of AHF were assessed and classified in four main groups: acute coronary syndrome, atrial fibrillation with rapid ventricular conduction, acute pulmonary disease (including chronic obstructive pulmonary disease exacerbation, asthma and pulmonary infection) and other causes. The latter group includes undetermined precipitating factors and all precipitating factors not fitting in the previous three categories. The diagnosis of AHF in this cohort has been previously shown to be highly accurate.[7] As detailed data about acute pulmonary disease were not included in the original database, the adjudication committee verified and confirmed the combination of AHF and acute pulmonary disease.[7] Follow-up visits were performed by phone contact at 1, 3, 6 and 12 months after hospital discharge. Hospital readmission during 90 days after hospital discharge and survival at 1 year after admission were analysed. All patients gave informed consent. The study was carried out in accordance with the Declaration of Helsinki and was approved by the institutional review board of each centre. This study was registered in clinicaltrials.gov, and the identifier is NCT01374880.

Statistic analysis

Group characteristics were compared with the Fisher's exact test or the Mann–Whitney *U* test, as appropriate. The effects of the presence compared with absence of every precipitating factor on 1 year mortality and 90 days readmission rates were assessed using Cox regression models without and with adjustment for potential confounding factors (age, sex and impaired renal function, defined as eGFR < 60 mL/min/1.73 m^2). Moreover, the effect of precipitating factors was assessed in the subgroups of patients older than 75 years and aged of 75 years or younger. Mortality and readmission were described with the Kaplan–Meier curve, and differences between groups were assessed by the log-rank test. The null hypothesis was rejected with a two-sided *P*-value < 0.05. All analyses were performed with the use of IBM SPSS Statistics, Version 21.0. (IBM Corp, Armonk, NY). Values are expressed as median (interquartile range) or as number (percentage), as appropriate.

Results

Population characteristics

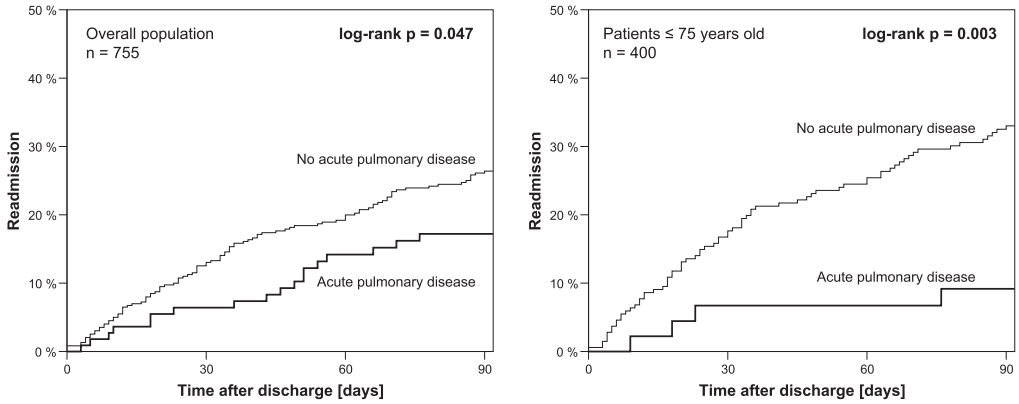
A total of 755 patients with AHF were included in the analysis. Population characteristics are summarized in *Table 1*. The median age was 75 (64–84) years, 56% of patients were men and clinical signs of congestion were commonly reported: the respiratory rate was 26 per minute (22–32 per minute), rales were audible during lung auscultation of 582 patients (82%), peripheral edema and jugular distention were reported in 431 (57%) and 310 (41%) patients, respectively. Concerning precipitating factors of AHF, acute coronary syndrome was present in 47 patients (6%), atrial fibrillation with

Table 2 Precipitating factors and risk of 90 days readmission

	Overall, unadjusted		Overall, adjusted		Patients ≤75 years, adjusted		Patients >75 years, adjusted	
Precipitating factor	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Atrial fibrillation	1.29 (0.83–2.00)	0.25	1.46 (0.93–2.29)	0.10	2.23 (1.29–3.85)	0.004	0.74 (0.33–1.67)	0.47
Acute coronary syndrome	1.38 (0.70–2.72)	0.35	1.36 (0.66–2.79)	0.40	2.23 (1.02–4.86)	0.044	0.34 (0.05–2.51)	0.29
Acute pulmonary disease	0.61 (0.37–0.99)	0.049	0.65 (0.39–1.08)	0.10	0.20 (0.06–0.63)	0.006	1.36 (0.72–2.56)	0.35
Other	1.12 (0.78–1.62)	0.54	0.99 (0.68–1.44)	0.95	0.98 (0.60–1.59)	0.92	1.02 (0.56–1.85)	0.95

AHF, acute heart failure; CI, confidence interval.
Risk of 90 days readmission in presence of predefined classes of precipitating factors of AHF compared with absence of the same factor. Adjustment was performed for age, sex and impaired renal function.

Figure 2 Readmissions of patients with acute heart failure precipitated by acute pulmonary disease compared with acute heart failure precipitated by non-pulmonary causes during 90 days after discharge in the overall population and in the subgroup of patients ≤75 years.



rapid ventricular response in 127 patients (17%) and acute pulmonary disease in 149 patients (20%). In 459 patients (61%), AHF was precipitated by other causes. Of note, in 27 patients (4%), a combination of acute coronary syndrome and atrial fibrillation was identified as precipitating factor.

Characteristics of patients with acute heart failure precipitated by acute pulmonary disease

As summarized in *Table 1*, patients with AHF precipitated by acute pulmonary disease were older (78 years vs. 73 years), reported more often previous history of chronic obstructive pulmonary disease or asthma (42% vs. 12%), suffered from greater respiratory impairment (higher respiratory rate and lower peripheral oxygen saturation) and showed more often wheezing on lung auscultation (44% vs. 13%) than patients with AHF precipitated by non-pulmonary causes. As illustrated in *Figure 1*, patients with AHF precipitated by acute pulmonary disease had higher levels of C-reactive protein [35 mg/L (10–110 mg/L) vs. 14 mg/L (5–31 mg/L), $P < 0.001$] but lower levels of BNP [899 pg/mL (404–1445 pg/mL) vs. 1191 pg/mL (643–2329 pg/mL), $P < 0.001$] compared with the group of AHF precipitated by non-pulmonary causes.

Precipitating factors of acute heart failure and readmission rates

Precipitating factors significantly influenced the 90 days readmission rates, as shown in *Table 2*. In the overall population, acute pulmonary disease was associated with lower readmission rates (hazard ratio (HR) 0.61, 95% confidence interval (CI) 0.37–0.99, $P = 0.049$), whereas atrial fibrillation with rapid ventricular response, acute coronary syndrome and other precipitating factors showed a non-significant trend towards higher readmission rates. After adjustment for potential confounding factors, none of the precipitating factors significantly influenced the readmission rates. As shown in *Figure 2* (left panel), the subgroup of patients with AHF precipitated by acute pulmonary disease ($n = 149$) showed fewer readmissions (log-rank $P = 0.047$) compared with the subgroup of patients with AHF precipitated by non-pulmonary causes ($n = 606$).

In the subgroup of patients aged 75 years or younger, differences were even more pronounced: as shown in *Table 2*, after adjustment for potential confounding factors, acute pulmonary disease was associated with markedly lower readmission rates (HR 0.20, 95% CI 0.06–0.63, $P = 0.006$), whereas atrial fibrillation (HR 2.23, 95% CI 1.29–3.85, $P = 0.004$) and acute coronary syndrome (HR 2.23, 95% CI 1.02–4.86,

Table 3 Precipitating factors and risk of 1 year mortality

	Overall unadjusted		Overall adjusted		Patients ≤75 years, adjusted		Patients >75 years, adjusted	
Factor	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Atrial fibrillation	0.66 (0.36–1.21)	0.18	0.63 (0.34–1.15)	0.13	0.50 (0.12–2.16)	0.35	0.67 (0.34–1.31)	0.24
Acute coronary syndrome	0.96 (0.42–2.19)	0.92	1.00 (0.44–2.29)	1.00	--[a]	0.98	1.49 (0.64–3.46)	0.35
Acute pulmonary disease	1.59 (1.04–2.43)	0.034	1.46 (0.94–2.25)	0.09	2.52 (1.17–5.41)	0.018	1.03 (0.61–1.75)	0.91
Other	0.90 (0.60–1.33)	0.59	0.95 (0.64–1.43)	0.82	0.72 (0.35–1.50)	0.38	1.06 (0.66–1.71)	0.81

AHF, acute heart failure; CI, confidence interval.
Risk of 1 year mortality in presence of predefined classes of precipitating factors of AHF compared with absence of the same factor. Adjustment was performed for age, sex and impaired renal function.
[a]No risk calculation possible because of lack of events in this subgroup.

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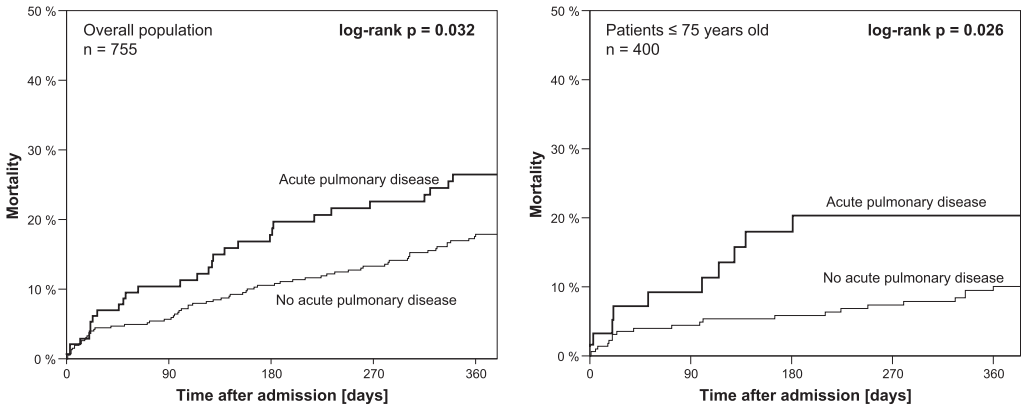
Figure 3 Mortality of patients with acute heart failure precipitated by acute pulmonary disease compared with acute heart failure precipitated by non-pulmonary causes during 1 year after admission in the overall population and in the subgroup of patients ≤75 years.



$P = 0.044$) were associated with higher readmission rates. As illustrated in *Figure 2* (right panel), younger patients with AHF precipitated by acute pulmonary disease showed fewer readmissions compared with the subgroup of patients with AHF precipitated by non-pulmonary causes (log-rank $P = 0.003$).

Precipitating factors of acute heart failure and survival at 1 year

As shown in *Table 3*, acute pulmonary disease at admission was associated with higher mortality at 1 year in the overall population (HR 1.59, 95% CI 1.04–2.43, $P = 0.034$), whereas all three other groups of precipitating factors were not. After adjustment for potential confounding factors, acute pulmonary disease showed only a non-significant trend towards higher risk of death in the overall population (HR 1.46, 95% CI 0.94–2.25, $P = 0.09$). As illustrated in *Figure 3* (left panel), patients with AHF precipitated by acute pulmonary disease showed increased mortality during 1 year follow-up compared with the subgroup of patients with AHF precipitated by non-pulmonary causes (log-rank $P = 0.032$).

More interestingly, in the subgroup of patients aged 75 years or younger, acute pulmonary disease was associated with significantly higher risk of death (HR 2.52, 95% CI 1.17–5.41, $P = 0.018$). As illustrated in *Figure 3* (right panel), younger patients with AHF precipitated by acute pulmonary disease showed higher mortality compared with the subgroup of patients with AHF precipitated by non-pulmonary causes (log-rank $P = 0.026$).

Discussion

The influence of precipitating factors on outcome, described in the present paper, extends the concept proposed by Fonarow and co-workers after analysis of the OPTIMIZE-HF registry.[2] Fonarow and co-workers showed an association between acute coronary syndrome (ACS), pulmonary infection and higher in-hospital mortality, but no data exist on the influence of precipitating factors on post-discharge readmissions and long-term mortality. The present study demonstrated that precipitating factors of AHF may substantially influence outcome far beyond the duration of hospitalization, especially in patients aged 75 years or younger: readmission rates were low when acute pulmonary disease precipitated AHF and high when non-acute pulmonary disease, including atrial fibrillation or acute coronary syndrome, precipitated AHF. Regarding long-term survival, acute pulmonary disease was also associated with higher mortality.

The influence of precipitating factors of AHF on post-discharge readmission rate, in patients aged 75 years or younger, is a novel observation. The existence of congestion is a frequent cause of hospital readmission in patients with chronic heart failure.[8] In the present study, the subgroup with acute pulmonary disease, as precipitating cause of AHF, showed lower levels of BNP suggesting a lower level of congestion compared with patients with non-pulmonary precipitating factors. Furthermore, patients with acute pulmonary diseases, including infections, once treated, are usually discharged home with rare readmissions. The influence of acute pulmonary disease on post-discharge readmission rate was mostly seen in patients aged 75 years or younger, while no influence of precipitating factors on readmissions in older AHF patients. We recently showed that effect of several prognostic factors was influenced by age and was more pronounced in AHF patients younger than 75 years, compared with the older ones.[6] Results of the present study confirm the stronger relationship between prognostic factors and outcome in younger patients, although the reasons remain unknown: a more complex interaction between precipitating factors, multimorbidity and frailty of older patients with AHF could be a reasonable explanation.

Surprisingly, the observed influence of acute pulmonary disease on long-term mortality was divergent from that on re-admission: patients with AHF exacerbated by acute pulmonary disease showed higher mortality. Two recently published studies showed that pneumonia is associated with increased risk for cardiovascular events after hospital discharge.[9,10] A combination of endothelial dysfunction, plaque instability, activated coagulation,[11] volume overload, inflammatory and ischemic myocardial injury[12] and arrhythmias[13] have been postulated to explain increased morbidity and mortality. It is still unclear whether the adverse prognosis of the subgroup of admitted for AHF precipitated by acute pulmonary disease is caused by the unfavourable association of AHF and pulmonary disease itself or is rather a marker of a more complex co-morbidity profile in patients with such an association.

Our study suggests that the peculiar pathophysiological background of AHF precipitated by acute pulmonary disease exposes those patients to increased risk of death despite fewer readmissions. As a consequence, those patients should benefit not only from aggressive initial treatment but also from a more intensive and interdisciplinary follow-up after hospital discharge.

Limitations

The study was conducted on a medium-sized cohort of patients with AHF from three tertiary centres. Therefore, the conclusions of this study should be confirmed in larger cohorts. However, this cohort was large enough to demonstrate significant differences between the different precipitating factors. Moreover, the group of 'other precipitating factors' was quite large, as our database was not conceived for further differentiation among other causes of AHF. This group might include patients with AHF precipitated by other causes as hypertension, malcompliance and worsening renal function.[3–5] Despite outcome data were derived from telephonic follow-up and relevant censoring (287 patients, 38%) occurred, the median follow-up in the cohort was 320 days. In addition, the cause of readmission was not assessed during follow-up, and therefore, the risk of a potential bias derived from new-onset precipitating factors, although small, cannot be excluded.

Conclusions

Precipitating factors of AHF substantially influence outcome after hospitalization. In particular, patients with AHF precipitated by acute pulmonary disease showed fewer readmissions and higher 1 year mortality, especially in patients aged 75 years or younger.

Conflict of interest

The authors declare that they have no competing interests.

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