ORIGINAL RESEARCH ARTICLE

Readmission following both cardiac and non-cardiac acute dyspnoea is associated with a striking risk of death

Kamilė Čerlinskaitė[1,2,3] [iD], Alexandre Mebazaa[2,3,4]*, Raphaël Cinotti[5], Michael Matthay[6,7], Desiree N. Wussler[8], Etienne Gayat[2,3,4], Vytautas Juknevičius[1,9], Nikola Kozhuharov[8], Julia Dinort[8], Eleni Michou[8], Danielle M. Gualandro[8], Eglė Palevičiūtė[1,9], Irina Alitoit-Marrote[9], Denis Kablučko[9], Loreta Bagdonaitė[10,11], Mindaugas Balčiūnas[1,9], Dovilė Vaičiulienė[12], Ieva Jonauskienė[12], Justina Motiejūnaitė[12], Kęstutis Stašaitis[12], Audrys Kukulskis[12], Šarūnas Damalakas[12], Aleksandras Laucevičius[1], Christian Mueller[8], Aušra Kavoliūnienė[12], Jelena Čelutkienė[1,9] and GREAT network

[1]*Clinic of Cardiac and Vascular Diseases, Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, Vilnius, Lithuania;* [2]*Inserm UMR-S 942, Cardiovascular Markers in Stress Conditions (MASCOT), Paris, France;* [3]*Department of Anesthesiology and Critical Care, Hôpitaux Universitaires Saint Louis-Lariboisière, Assistance Publique des Hopitaux de Paris, 2 Rue Ambroise Paré, Paris, 75010, France;* [4]*Université de Paris, Paris, France;* [5]*Department of Anesthesia and Critical Care, Hôpital Laennec, University Hospital of Nantes, Saint-Herblain, France;* [6]*Department of Medicine and Anesthesia, University of California, San Francisco, CA, USA;* [7]*Cardiovascular Research Institute, University of California, San Francisco, CA, USA;* [8]*Cardiology Department and Cardiovascular Research Institute Basel (CRIB), University Hospital Basel, University of Basel, Basel, Switzerland;* [9]*Centre of Cardiology and Angiology, Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania;* [10]*Institute of Biomedical Science, Faculty of Medicine, Vilnius University, Vilnius, Lithuania;* [11]*Centre of Laboratory Medicine, Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania; and* [12]*Lithuanian University of Health Sciences, Kaunas, Lithuania*

Abstract

Aims   Readmission and mortality are the most common and often combined endpoints in acute heart failure (AHF) trials, but an association between these two outcomes is poorly investigated. The aim of this study was to determine whether unplanned readmission is associated with a greater subsequent risk of death in patients with acute dyspnoea due to cardiac and non-cardiac causes.

Methods and results   Derivation cohort (1371 patients from the LEDA study) and validation cohort (1986 patients from the BASEL V study) included acute dyspnoea patients admitted to the emergency department. Cox regression analysis was used to determine the association of 6 month readmission and the risk of 1 year all-cause mortality in AHF and non-AHF patients and those readmitted due to cardiovascular and non-cardiovascular causes. In the derivation cohort, 666 (49%) of patients were readmitted at 6 months and 282 (21%) died within 1 year. Six month readmission was associated with an increased 1 year mortality risk in both the derivation cohort [adjusted hazard ratio (aHR) 3.0 (95% confidence interval, CI 2.2–4.0), $P < 0.001$] and the validation cohort (aHR 1.8, 95% CI 1.4–2.2, $P < 0.001$). The significant association was similarly observed in AHF (aHR 3.2, 95% CI 2.1–4.9, $P < 0.001$) and other causes of acute dyspnoea (aHR 2.9, 95% CI 1.9–4.5, $P < 0.001$), and it did not depend on the aetiology [aHR 2.2, 95% CI 1.6–3.1 for cardiovascular readmissions; aHR 4.1, 95% CI 2.9–5.7 for non-cardiovascular readmissions ($P < 0.001$ for both)] or timing of readmission.

Conclusions   Our study demonstrated a long-lasting detrimental association between readmission and death in AHF and non-AHF patients with acute dyspnoea. These patients should be considered 'vulnerable patients' that require personalized follow-up for an extended period.

Introduction

Acute dyspnoea, due to cardiac or non-cardiac causes, is one of the chief complaints in the emergency department (ED) and cardiac intensive care unit and is associated with poor short-term and long-term outcomes.[1–8] In acute heart failure (AHF), the immediate post-discharge period is described as the 'vulnerable phase' that corresponds to high readmission and death rates within a few months after discharge.[9] Thus, reduction in readmission and/or death are the most frequent efficacy endpoint in AHF trials.[10,11] However, though often combined in recent trials, whether unscheduled readmission and subsequent death are associated remains poorly investigated.[12–14] Also, the vulnerable phase has not been described in large population of patients with acute dyspnoea including AHF and non-AHF groups.

We aimed to evaluate the relationship between readmission and the risk of death in acute dyspnoea patients after discharge and to compare this association between AHF and other causes of dyspnoea using large cohorts from two European countries.

Methods

Study design

We analysed two independent acute dyspnoea cohorts for derivation and validation purposes.

Derivation cohort

Derivation cohort was derived from LEDA (Lithuanian Echocardiography Study of Dyspnoea in Acute Settings, ClinicalTrials.gov: NCT03048032) prospective observational multicentre study, performed in two Lithuanian university centres in collaboration with a research protocol of international GREAT (Global Research on Acute Conditions Team) network. The study enrolled patients from March 2015 to December 2017. A 1 year follow-up was completed in December 2018. The study was approved by the Lithuanian Bioethics Committee (No. L-15-01) and conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent.

Inclusion criteria Consecutive adult patients admitted to the ED with chief complaint of acute dyspnoea due to any cause were included.

Exclusion criteria Patients with acute coronary syndrome suspected during the first 4 h of admission were excluded. If the patients were admitted more than once, only the first episode was taken as index admission. Further exclusion criteria were in-hospital mortality or organ transplantation during index admission or readmission.

Data collection Patient demographic data, co-morbidities, baseline medication, clinical signs and laboratory parameters at admission, early in-hospital treatment, medication at discharge, and in-hospital death were recorded.[15] Patient sex was self-reported. The severity of dyspnoea at admission was assessed using subjective Borg scale.[16] Blood samples were taken within 4 h of presentation, frozen at −80°C, and sent to the Inserm UMR-942 institute for measurements of N-terminal pro-B-type natriuretic peptide and high-sensitivity troponin T (Roche Diagnostics® GmbH, Mannheim, Germany).

Validation cohort

Validation cohort was derived from BASEL V (Basics in Acute Shortness of Breath EvaLuation Study, ClinicalTrials.gov: NCT01831115) prospective multicentre observational study. Enrolment period and inclusion/exclusion criteria have been reported elsewhere.[17] Briefly, adult patients with acute, non-traumatic dyspnoea presenting to the ED were enrolled into the study from 2006 to 2014 in two university centres in Switzerland. Patients on haemodialysis were excluded. The study was approved by the local ethical committee and carried out according to the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Diagnosis adjudication

In the derivation cohort, teams of three cardiologists blinded to post-discharge outcomes adjudicated the cause of acute dyspnoea. All available patient records including medical history, symptoms and signs at admission, previous or admission natriuretic peptides, routine laboratory measurements, and echocardiography were reviewed. Final diagnoses were classified as AHF or non-AHF; the latter included chronic obstructive pulmonary disease (COPD)/asthma exacerbation, pulmonary embolism, pulmonary/non-pulmonary infections, and cancer, among others. Central adjudication of the diagnosis in the validation cohort has been previously described.[17]

Readmission and mortality

Derivation cohort

All patients were followed up for 1 year after discharge. Lithuanian administrative databases provided data on mortality and unplanned all-cause readmissions coded by the 10th Revision of the International Classification of Diseases. Lithuania's national administrative databases capture all of the events because there are no private hospitals that admit

acute patients and are not covered by healthcare insurance. Therefore, there were no patients lost to follow-up.

Validation cohort

Patients were contacted by telephone at 3 and 6 months and 1 year after the index episode.[17] In case of uncertainties, referring physicians and administrative databases were approached.

Study endpoints

The primary endpoint was the association between the first all-cause readmission within 6 months after discharge and 1 year all-cause mortality in patients with AHF and non-AHF causes of dyspnoea.

Secondary endpoints were as follows:

i the association between the first readmissions due to cardiovascular (CV) vs. non-cardiovascular (non-CV) causes within 6 month and 1 year mortality;

ii the association between the first readmissions within 6 month and 1 year mortality in different subgroups, based on age, sex, co-morbidities, causes of dyspnoea, and biomarker levels.

Statistical analysis

Continuous variables are presented as median and inter-quartile ranges, and categorical variables are presented as counts (percentage). The differences between study groups were compared using Kruskal–Wallis test for continuous variables and χ^2 test for the categorical variables.

To investigate the impact of 6 month readmission on 1 year mortality, an unadjusted and adjusted Cox regression analysis was performed comparing non-readmitted and readmitted patients. To investigate if the precise timing of the first readmission influenced 1 year mortality, the same analyses were performed that compared non-readmitted and readmitted patients at three periods (first month, second and third months, and fourth to sixth months after discharge). First, the analysis was performed in all patients, comparing survival between patients readmitted and not readmitted during the first month. Then, data were censored by removing patients who either died or were readmitted during the first month. The same analysis was then repeated in patients readmitted and not readmitted during second and third months and, finally, in the same manner in patients readmitted and not readmitted between the fourth and sixth months. Multivariate Cox regression included criteria known to affect prognosis: age, sex, co-morbidities (history of heart failure, coronary artery disease, and diabetes), systolic blood pressure, heart rate, estimated glomerular filtration rate <60 mL/min/1.73 m^2, and sodium <136 mmol/L.[15] The analysis described earlier was repeated in the AHF and non-AHF

groups and for CV or non-CV readmissions against non-readmitted patients as the reference group.

Subgroup analysis was performed by conducting unadjusted Cox regression analyses dividing patients by age (>65 and ≤65 years old), sex, history of heart failure, aetiology of acute dyspnoea, N-terminal pro-B-type natriuretic peptide (>1000 and ≤1000 ng/L),[18] high-sensitivity troponin T (>14 and ≤14 ng/L), and left ventricular ejection fraction (>50% and ≤50%) measurements.

Sensitivity analysis was performed by conducting unadjusted and adjusted Cox regression omitting patients who died prior to the analysed readmission follow-up point; for example, when analysing association of 6 month readmission with 1 year mortality, only patients who survived the first 6 months after discharge were analysed.

All statistical analyses were performed using R Version 3.5.3 (The R Foundation for Statistical Computing, Vienna, Austria) with the statistical packages 'survival' for survival analyses and 'icd' to decode causes of death and readmission.[19,20] All tests were two sided, and a *P* value of <0.05 was considered significant. No imputation was used for missing data.

Results

Derivation cohort

Demographic and clinical data

The LEDA study enrolled 1566 patients (Supporting Information, *Figure S1*). After excluding duplicate, transplanted patients and those who died in the hospital during the index admission, 1371 (87.5%) patients were included in the analysis (median age 71 [61–79] years and 599 (43.6%) female). Baseline characteristics are described in *Table 1*.

During the 6 months after discharge, 666 (48.6%) patients were readmitted, 379 (56.9%) for CV and 287 (43.1%) for non-CV causes (*Figure 1A*). Readmitted patients were older and had more co-morbidities, higher heart rate, higher concentrations of cardiac, renal, and inflammatory biomarkers, and lower haemoglobin (*Table 1*).

The characteristics of the 731 (53.3%) AHF and 640 (46.7%) non-AHF patients are described in Supporting Information, *Tables S1* and *S2*. In the first months after discharge (*Figure 1B* and *1C*), readmission rate in AHF and non-AHF groups was similarly high, whereas at 6 months, AHF patients were readmitted more frequently (53.5% vs. 43%, respectively, *P* < 0.001). In AHF patients, CV causes of readmission dominated (68.3%), in contrast to non-AHF patients (59.3% non-CV readmissions). Furthermore, the aetiology of readmission (CV or not) was often the same as the causes of index admission (*Figure 2*).

Table 1 Baseline characteristics, treatment at discharge, and outcomes of the derivation LEDA cohort

	Total (N = 1371)	Readmitted at 6 months (N = 666)	Non-readmitted at 6 months (N = 705)	P value	n
Age, median [IQR]	71 [61–79]	72 [64–79]	69 [59–78]	0.001	1371
Female sex, n (%)	599 (43.7%)	276 (41.4%)	323 (45.8%)	0.115	1371
AHF, n (%)	731 (53.3%)	391 (58.7%)	340 (48.2%)	<0.001	1371
Co-morbidities, n (%)					
History of chronic heart failure	829 (61.5%)	441 (67.5%)	388 (55.7%)	<0.001	1349
Hypertension	1068 (79.2%)	530 (81.2%)	538 (77.3%)	0.093	1349
Diabetes mellitus	310 (23%)	169 (25.9%)	141 (20.3%)	0.017	1349
Coronary artery disease	467 (34.6%)	246 (37.7%)	221 (31.8%)	0.026	1349
COPD	179 (13.3%)	93 (14.2%)	86 (12.4%)	0.347	1349
Asthma	82 (6.1%)	38 (5.8%)	44 (6.3%)	0.786	1349
Active or recent cancer	175 (13%)	105 (16.1%)	70 (10.1%)	0.001	1349
Anaemia	481 (35.7%)	251 (38.4%)	230 (33.0%)	0.044	1349
Medications at admission, n (%)					
ACEi/ARB	625 (46.4%)	312 (47.9%)	313 (45%)	0.315	1348
Beta-blockers	686 (50.9%)	346 (53.1%)	340 (48.9%)	0.135	1348
Diuretics[a]	585 (43.4%)	311 (47.7%)	274 (39.4%)	0.002	1348
Aldosterone antagonists	226 (16.8%)	126 (19.3%)	100 (14.4%)	0.018	1348
Inhaled steroids	76 (5.6%)	34 (5.2%)	42 (6%)	0.593	1348
β_2 mimetics	110 (8.2%)	54 (8.3%)	56 (8%)	0.953	1348
Anti-diabetics	172 (12.8%)	97 (14.9%)	75 (10.8%)	0.03	1348
Clinical parameters at admission, median [IQR]					
BMI (kg/m²)	29.5 [25.6–34.5]	29.7 [25.5–34.6]	29.4 [25.6–34.4]	0.656	779
Borg scale of dyspnoea severity	7 [5–8]	7 [5–8]	7 [5–8]	0.039	1139
Duration of dyspnoea (days)	6 [1–14]	7 [1–14]	5 [1–14]	0.236	1085
Systolic blood pressure (mmHg)	140 [125–160]	139 [124–159]	140 [125–160]	0.093	1345
Heart rate (b.p.m.)	88 [74–104]	90 [75–107]	85 [72–101]	0.025	1073
Respiratory rate	20 [16–22]	20 [16–22]	20 [16–22]	0.275	665
SpO2 (%)	94 [90–96]	93 [89–96]	94 [90–96]	0.164	1002
Laboratory parameters, median [IQR]					
NT-proBNP (ng/L)	1957 [438–5289]	2604 [691–6542]	1410 [322–3980]	<0.001	813
hs-TnT (ng/L)	30 [10–50]	30 [20–50]	20 [10–40]	<0.001	812
BNP (ng/L)	387 [139.5–1103]	513 [178.5–1284.5]	321 [109–1019]	0.001	683
Creatinine (μmol/L)	93 [75–121]	98 [77–134]	89 [74–112]	<0.001	1270
eGFR (mL/min/1.73 m²)	62 [45–79]	58 [41–75]	64 [48–80]	<0.001	1270
eGFR < 60 mL/min/1.73 m², n (%)	605 (47.6%)	326 (52.9%)	279 (42.7%)	<0.001	1270
CRP (mg/L)	9.4 [3.4–31.2]	10.6 [4.0–34.1]	8.6 [2.8–26.7]	0.003	1131
HGB (g/dL)	13.1 [11.7–14.4]	13.0 [11.5–14.3]	13.3 [11.9–14.5]	0.015	1293

(Continues)

Table 1 (continued)

|	Total (N = 1371)	Readmitted at 6 months (N = 666)	Non-readmitted at 6 months (N = 705)	P value	n
Blood glycaemia (mmol/L)	6.2 [5.5–7.4]	6.4 [5.5–7.65]	6.1 [5.4–7.3]	0.018	1000
Treatment at discharge, n (%)					
ACEi/ARB	724 (54.2%)	359 (55.5%)	365 (52.9%)	0.371	1337
Beta-blockers	804 (60.1%)	395 (61.1%)	409 (59.3%)	0.544	1337
Diuretics[a]	773 (57.8%)	402 (62.1%)	371 (53.8%)	0.002	1337
Aldosterone antagonists	365 (27.3%)	196 (30.3%)	169 (24.5%)	0.02	1337
Inhaled steroids	91 (6.8%)	43 (6.6%)	48 (7%)	0.907	1337
$β_2$ mimetics	125 (9.3%)	62 (9.6%)	63 (9.1%)	0.849	1337
Anti-diabetics	201 (15%)	109 (16.8%)	92 (13.3%)	0.085	1337
Outcomes					
Hospitalized, n (%)	808 (58.9%)	420 (63.1%)	388 (55%)	0.003	1371
LOS, median [IQR]	9 [7–13]	9 [7–13]	9 [7–13]	0.994	808[b]
Death at 12 months, n (%)	282 (20.6%)	211 (31.7%)	71 (10.1%)	<0.001	1371

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; AHF, acute heart failure; BMI, body mass index; BNP, B-type natriuretic peptide; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HGB, haemoglobin; hs-TnT, high-sensitivity troponin T; IQR, inter-quartile range; LOS, length of stay; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide.
Baseline characteristics, treatment at discharge, and outcomes in acute dyspnoea overall population and patients readmitted and not readmitted at 6 months. Data are presented as medians [IQR] or counts (%).
[a]Any diuretic.
[b]Only hospitalized patients.

Figure 1 Rates of unplanned all-cause first hospital readmission in the first 6 months in (A) acute dyspnoea (*n* = 1371), (B) acute heart failure (AHF) (*n* = 731), and (C) non-AHF (*n* = 640) patients of the derivation LEDA cohort. CV, cardiovascular; NCV, non-cardiovascular.
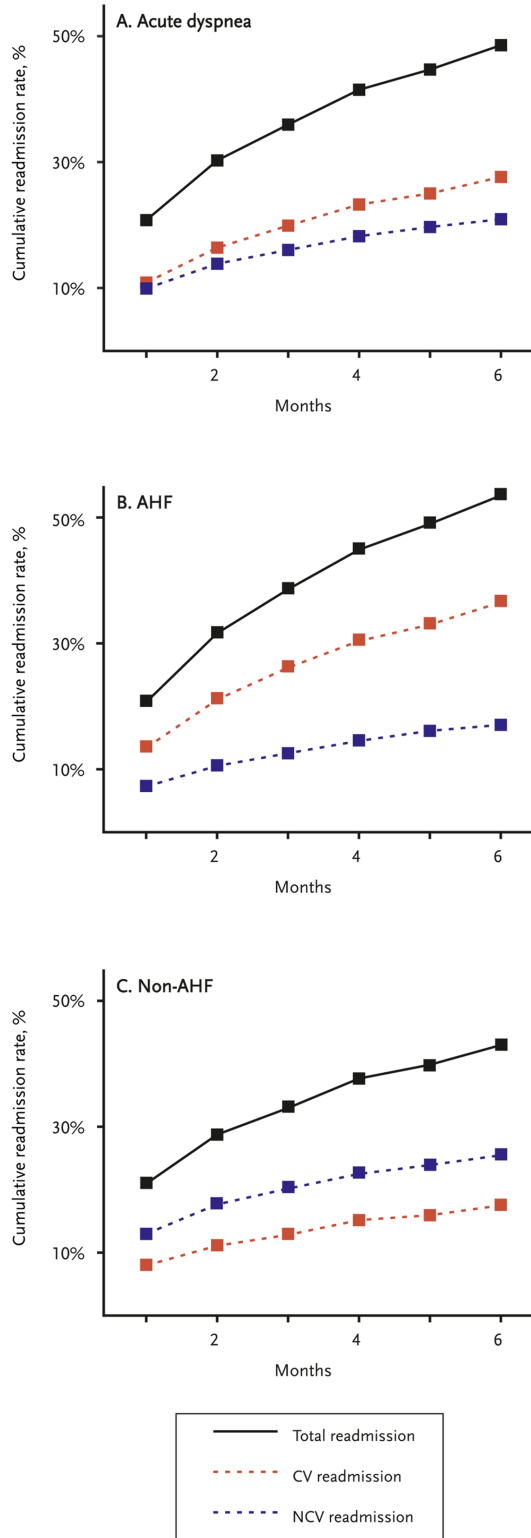
Primary endpoint

The 1 year mortality was 20.6% (282 patients). Patients readmitted within 6 months died three times more frequently than non-readmitted patients [211 (31.7%) vs. 71 (10.1%), respectively, *P* < 0.001]. The first episode of readmission within 6 months was associated with a three-fold risk of 1 year all-cause mortality [adjusted hazard ratio (aHR) 3.0, 95% confidence interval (CI) 2.2–4.0, *P* < 0.001] [*Figure 3* (IA)]. Furthermore, the mortality risk was consistently high, whether the first readmission occurred in the first month (aHR 2.9, 95% CI 2.2–3.8, *P* < 0.001) or later: in the second and third months (aHR 4.0, 95% CI 2.7–5.8, *P* < 0.001) or in the fourth to sixth months (aHR 2.8, 95% CI 1.6–4.9, *P* < 0.001).

One year all-cause mortality was equally high in patients with AHF or non-AHF (20% vs. 21.2%, respectively, *P* = 0.61). Readmitted patients died much more frequently than non-readmitted patients in both the AHF [117 (29.9%) vs. 29 (8.5%), *P* < 0.001] and the non-AHF [94 (34.2%) vs. 42 (11.5%), *P* < 0.001] groups. Readmission within 6 months was associated with similarly increased risk of 1 year mortality in both AHF and non-AHF groups [aHR 3.2, 95% CI 2.1–4.9, *P* < 0.001, and aHR 2.9, 95% CI 1.9–4.5, *P* < 0.001, respectively, *Figure 3* (IB)]. The detrimental association between readmission and death was persistently high at Month 1, Months 2 and 3, and Months 4–6 in both AHF and non-AHF groups (*P* for interaction >0.05 for all periods) [Supporting Information, *Figure S2* (IA)].

Secondary endpoints

Figure 3 (C) shows that CV or non-CV causes of readmission were both associated with an increased risk of 1 year mortality [aHR 2.2, 95% CI 1.6–3.1, and aHR 4.1, 95% CI 2.9–5.7, respectively (*P* < 0.001 for both)], also at any time of readmission within the first 6 months after discharge [Supporting Information, *Figure S2* (IB)].

Subgroup and sensitivity analysis

The association between the first 6 month readmission and higher risk of 1 year mortality remained consistent throughout all studied subgroups [*Figure 4* (I)]. Furthermore, the relationship between readmission and mortality remained significant in all time periods in the sensitivity analysis, performed in the subgroup of patients who survived first 6 months after discharge (Supporting Information, *Table S3*).

Validation cohort

The validation cohort included 1986 patients of the BASEL V study discharged alive with 1 year follow-up (median age 74 [61–82] years, 888 [44.7%] female, and 50% AHF) (Supporting Information, *Figure S3*). There were 812 (40.9%) patients readmitted at 6 months with 348 (42.9%) readmitted for CV and 464 (57.1%)—for non-CV causes. Characteristics of the

Figure 2 Trajectory of acute dyspnoea patients within 12 months after index admission in the LEDA derivation cohort. Almost half of the patients were readmitted at 6 months. A small percentage of patients died without being readmitted at 6 months (in purple). Patients who were readmitted died strikingly more frequently at 1 year than patients who were not readmitted at 6 months (32% vs. 10%, respectively, P < 0.001). Red = (re)admitted due to cardiovascular (CV) causes; blue = (re)admitted due to non-CV causes; green = survived without readmission; purple = died. AHF, acute heart failure. *Died at 6 months without readmission.
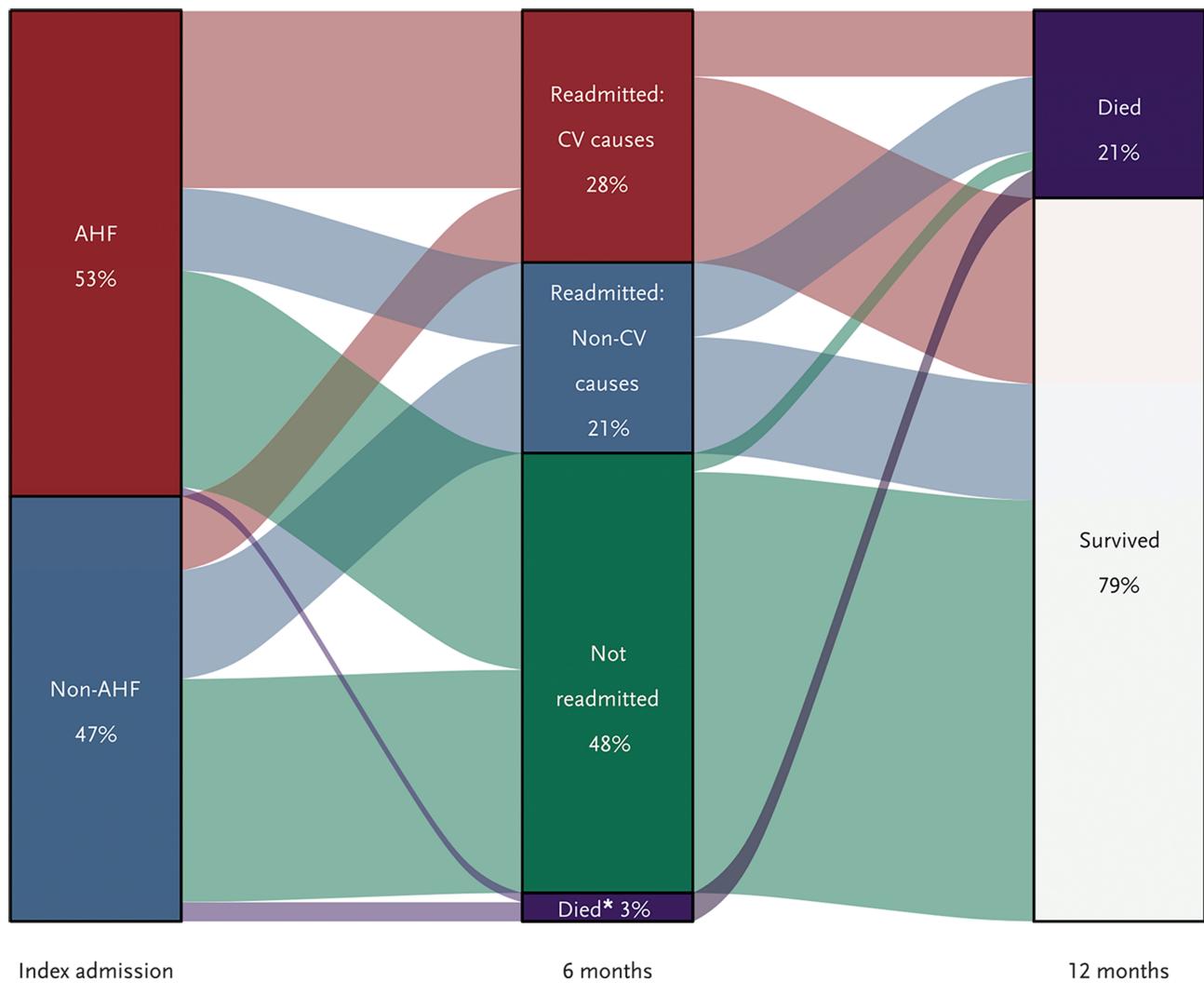
cohort are described in Supporting Information, *Table S4*. AHF patients were readmitted more frequently than non-AHF patients (45.9% vs. 35.9%, respectively, P < 0.001). In AHF patients, 62.1% readmissions were for CV causes, whereas 81.7% of readmitted non-AHF patients were readmitted for non-CV causes.

The total 1 year mortality was 19% (377 patients). Patients readmitted within 6 months died significantly more often than non-readmitted patients [218 (26.8%) vs. 159 (13.5%), respectively, P < 0.001]. *Figure 3* (IIA) shows that 6 month readmission in the validation cohort was also significantly associated with an increased risk of 1 year mortality in acute dyspnoea patients (aHR 1.8, 95% CI 1.4–2.2, P < 0.001). This relationship was uniform irrespective of the timing of

readmission, aetiology of index admission, and first readmission, except for the first month readmission in AHF patients and CV readmission [*Figure 3* (IIA and IIB) and Supporting Information, *Figure S2* (IIA and IIB)]. Subgroup analysis of the validation cohort is shown in *Figure 4* (II), and sensitivity analysis is presented in Supporting Information, *Table S5*.

Discussion

Our study clearly demonstrates long-lasting detrimental relationship between readmission and risk of death in AHF, as well as in non-AHF patients. Half of the patients presenting

Figure 3 Primary and secondary endpoints: relationship between all-cause readmissions and 1 year all-cause mortality in (I) derivation LEDA and (II) validation BASEL V cohorts. The figure depicts Cox hazard proportional regression results adjusted with age, gender, co-morbidities (history of chronic heart failure, coronary artery disease, and diabetes mellitus), systolic blood pressure, heart rate, creatinine, and sodium <136 mmol/L. The size of the point represents sample size of readmitted patients in a group. (A) Risk of death depending on the exact time or readmission. (B) First readmission in any time in the 6 months following index admission in acute heart failure (AHF) and non-AHF groups. (C) Analysis for cardiovascular (CV) and non-CV causes of readmissions. aHR, adjusted hazard ratio; CI, confidence interval.
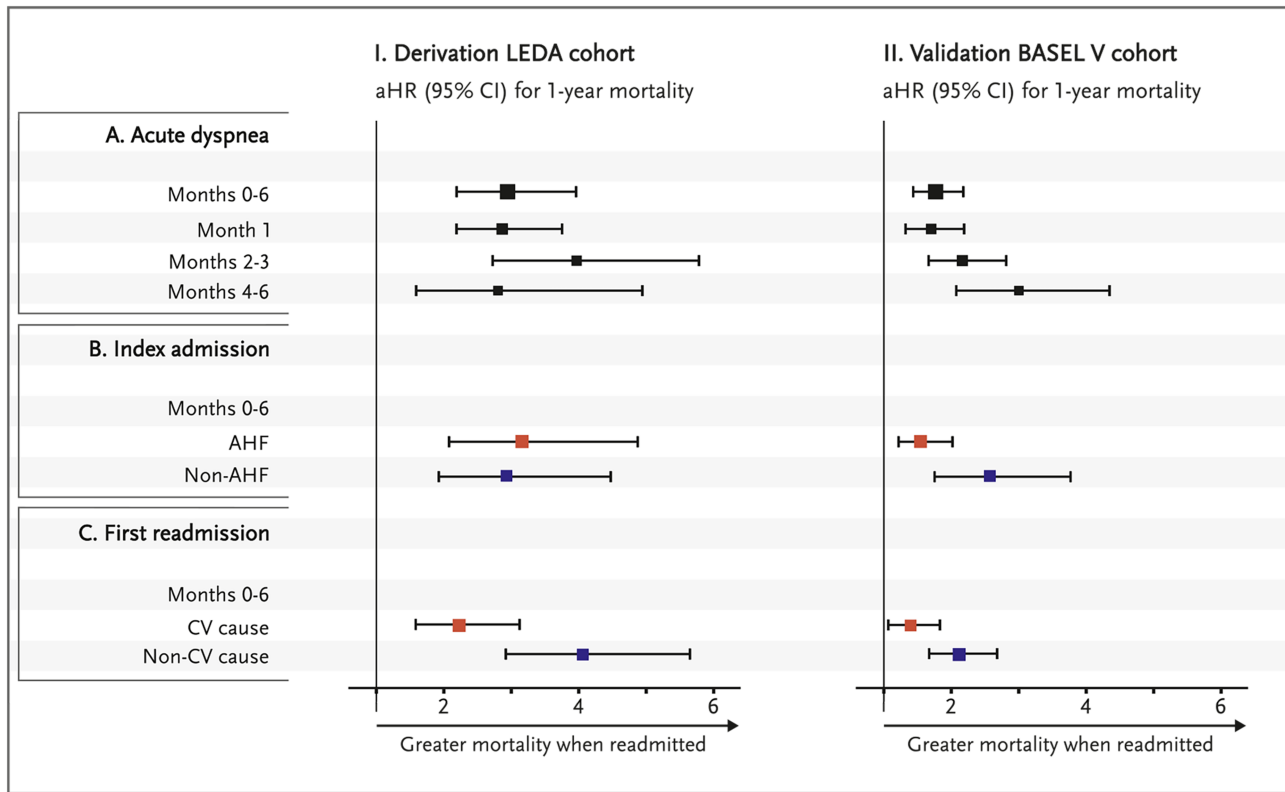
with acute dyspnoea were readmitted in the following months for similar causes as index admissions, and every readmission was associated with a striking risk of death.

Our study examined the link between readmission and mortality in the two largest contemporary cohorts of consecutive patients admitted with acute dyspnoea, with long-term follow-up, namely, LEDA and BASEL V. There were almost no patients lost to follow-up in both cohorts. Distribution of diagnoses, rates of readmission, and mortality were similar in both cohorts and comparable with those reported previously.[4,21,22] Despite some discrepancy, the two-fold to three-fold increase in the risk of 1 year mortality in patients readmitted after an acute dyspnoea event was found in both cohorts in two different regions of Europe with different income and healthcare systems and at different time frames.
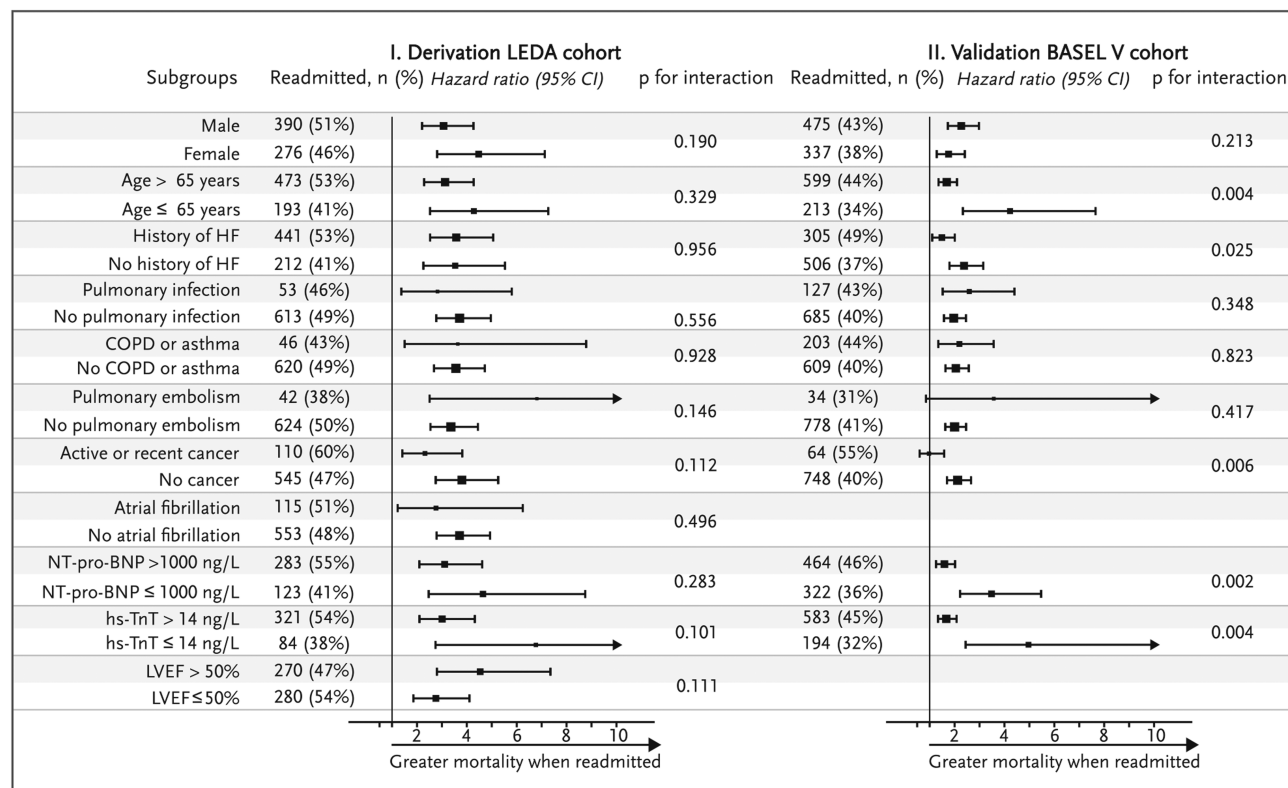
Even with emerging diagnostic strategies, such as natriuretic peptides testing and fast imaging techniques, acute dyspnoea remains a tremendous clinical challenge to treating physicians. It has been suggested that uncertainty in diagnosis and aetiology of acute dyspnoea may be associated with

longer length of stay and increased risk of mortality and readmission.[23] Our study demonstrated that, regardless of the underlying cardiac or non-cardiac cause, a strikingly high number of patients who had an ED visit for acute dyspnoea returned to the hospital: one-fifth in 1 month and one-half at 6 months. Such high rate of readmission in a short time frame is unique in medicine. For example, chest pain, another common ED complaint, is associated with a much lower rate of readmission.[24] Altogether, our results suggest that readmission may be linked to the persistent underlying disease despite seemingly resolved symptoms.[25] There is an urgent need of randomized trials investigating if diagnostic work-up and short and long-term personalized management of patients with acute dyspnoea including biomarkers and/or lung ultrasound could improve prognosis of this heterogeneous patient group. Our data also urge, in case of heart failure, the rapid implementation of guideline-recommended therapies.[26,27]

A growing interest in readmission has been observed in recent years due to US healthcare policies designed to reduce 30 day readmission rates of some acute CV and pulmonary

Figure 4 Secondary endpoint: the relationship between all-cause readmission and 1 year all-cause mortality in the subgroups of (I) derivation LEDA and (II) validation BASEL V cohorts. The size of the point represents the readmitted sample size in a group. CI, confidence interval; COPD, chronic obstructive pulmonary disease; HF, heart failure; hs-TnT, high-sensitivity troponin T; LVEF, left ventricular ejection fraction; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide.

Subgroups	I. Derivation LEDA cohort			II. Validation BASEL V cohort		
	Readmitted, n (%)	Hazard ratio (95% CI)	p for interaction	Readmitted, n (%)	Hazard ratio (95% CI)	p for interaction
Male	390 (51%)		0.190	475 (43%)		0.213
Female	276 (46%)			337 (38%)		
Age > 65 years	473 (53%)		0.329	599 (44%)		0.004
Age ≤ 65 years	193 (41%)			213 (34%)		
History of HF	441 (53%)		0.956	305 (49%)		0.025
No history of HF	212 (41%)			506 (37%)		
Pulmonary infection	53 (46%)		0.556	127 (43%)		0.348
No pulmonary infection	613 (49%)			685 (40%)		
COPD or asthma	46 (43%)		0.928	203 (44%)		0.823
No COPD or asthma	620 (49%)			609 (40%)		
Pulmonary embolism	42 (38%)		0.146	34 (31%)		0.417
No pulmonary embolism	624 (50%)			778 (41%)		
Active or recent cancer	110 (60%)		0.112	64 (55%)		0.006
No cancer	545 (47%)			748 (40%)		
Atrial fibrillation	115 (51%)		0.496			
No atrial fibrillation	553 (48%)					
NT-pro-BNP >1000 ng/L	283 (55%)		0.283	464 (46%)		0.002
NT-pro-BNP ≤ 1000 ng/L	123 (41%)			322 (36%)		
hs-TnT > 14 ng/L	321 (54%)		0.101	583 (45%)		0.004
hs-TnT ≤ 14 ng/L	84 (38%)			194 (32%)		
LVEF > 50%	270 (47%)		0.111			
LVEF ≤ 50%	280 (54%)					

Greater mortality when readmitted

diseases by using financial incentives.[28–30] Indeed, a low rate of 30 day readmission has been acknowledged as a key quality indicator of patient management during index hospitalization. A small number of studies showed that 30 day readmission was associated with greater mortality in AHF, COPD, or elderly patients.[12–14,31] Our study confirmed and extended the detrimental relationship between readmission and the risk of death in patients with acute dyspnoea to at least 6 months. The relationship between readmission and mortality was found not only in AHF but also in other causes of acute dyspnoea. Indeed, our data showed that, despite several differences including age and co-morbidities, acute respiratory failure associated with AHF, pulmonary infection, or decompensated COPD carried an equally high risk of death after readmission. Accordingly, this finding strongly suggests that index admission and subsequent readmissions are a continuum in patients for whom the underlying cardiac and/or pulmonary dysfunction(s) have not been resolved. In our study, impaired oxygenation and high C-reactive protein were common findings in both heart failure and non-heart failure patients and might be potential drivers of unfavourable prognosis.

A 'vulnerable' phase has been described in AHF patients as an early and transient post-discharge period with high rates of readmission and mortality.[9] Yet our results do not support the concept of a transient vulnerable phase neither in AHF nor in non-AHF patients. Alternatively, this study indicates that a patient who visits the ED with acute respiratory distress should instead be considered a 'vulnerable patient' even if dyspnoea is relieved, likely for a long period after discharge and possibly forever.

The present study has a few limitations. The study analysed two European cohorts; therefore, the results may not be applicable in other continents. Furthermore, because the LEDA protocol was designed to collect the clinical data at admission, data on patients' status and biology at discharge or during follow-up were not recorded. In addition, due to observational nature of the cohorts, there are some missing data. It has been noted that in a significant proportion of AHF patients, the main complaint may not be acute dyspnoea but a predominant peripheral congestion, which also has a poor prognosis,[32] so these patients might not have been included in our study. Also, a larger proportion of AHF patients did not receive diuretic on admission and/or discharge in LEDA

cohort compared with specialized heart failure registry data (a difference of more than 10%).[33] The patients were undertreated in terms of neurohormonal blockers on admission and/or discharge as well. This might reflect that a wide spectrum of cardiologists and internists treated patients in our study and there could have been different congestion evaluation and treatment strategies between them and dedicated heart failure specialists who participate in registries. Our study also emphasizes the need of the adjudication committee because differences in the diagnosis between adjudication committee and treating physician could also explain this discrepancy. Nonetheless, our study results demonstrate that regardless if there were some discrepancies in initial diagnoses, the result remained similar independently from adjudicated cause of acute dyspnoea, cause of readmission, and throughout all analysed subgroups, and it applies to any acute dyspnoea patient.

In summary, our study demonstrated the long-lasting detrimental association between readmission and death in AHF and non-AHF patients admitted to the ED with acute breathlessness. Although breathlessness is usually relieved at discharge, patients should be considered 'vulnerable patients' that require personalized follow-up, including the rapid implementation of guideline-recommended therapies in AHF patients.

Conflict of interest

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf. K.Č., A.M., V.J., E.P., I.M., D.K., L.B., M.B., D.V., I.J., J.M., K.S., Audrys K., Š.D., A.L., Aušra K., and J.Č. declare that they received financial support from Research Council of Lithuania for the submitted work. A.M. received speaker's honoraria from Orion, Otsuka, Philips, Roche, and Servier. A.M. received fee as a member of advisory board and/or steering committee and/or research grant from Adrenomed, Epygon, Neurotronik, Roche, Sanofi, and Sphyngotec. A.M. owns shares in S-Form Pharma. M.M. reports grants from NIH/NHLBI, Department of Defence, NIH/FDA, Bayer Pharmaceuticals, and GlaxoSmithKline and personal fees from CS Berhling, Boerhinger Ingelheim, Cerus Therapeutics, Roche Genentec, Quark Pharmaceuticals, and Thesan Pharamceuticals, outside the submitted work. E.G. received research grants from Sphingotec, Deltex Medical, and Retia Medical and consultancy fees from Magnisense, Roche Diagnostics, and Adrenomed. C.M. has received research support from the Swiss National Science Foundation, the Swiss Heart Foundation, the Kommission für Technologie und Innovation, the Stiftung für kardiovaskuläre Forschung Basel, Abbott, Alere, Amgen, AstraZeneca, Beckman Coulter, Biomerieux, Brahms, Roche, Siemens, Singulex, Sphingotec, the University of Basel, and the University Hospital Basel, as well as speaker honoraria/consulting honoraria from Abbott, Alere, AstraZeneca, Biomerieux, Boehringer Ingelheim, BMS, Brahms, Cardiorentis, Novartis, Roche, Siemens, Sanofi, and Singulex. Aušra K. received speaker honoraria from Servier, Bayer, Berlin-Chemie Menarini, Pfizer, and KRKA. Audrys K. received fee as member of Steering Committee Cardiorentis, Novartis, and Servier. J.Č. received investigator and speaker fees from Sanofi, Amgen, Novartis, Roche Diagnostics, Servier, and AstraZeneca. Other authors declared no conflicts of interest.

data collection, analysis and interpretation, writing the paper, and the decision to submit the paper for publication.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Baseline characteristics of the derivation LEDA cohort.
Table S2. Early treatment in the emergency department, treatment at discharge and outcomes of the LEDA derivation cohort.
Table S3. Sensitivity analysis of the derivation LEDA cohort.
Table S4. Baseline characteristics and outcomes of the validation BASEL V cohort.
Table S5. Sensitivity analysis of the validation BASEL V cohort.
Figure S1. Patient flowchart of the derivation LEDA cohort.
Figure S2. Secondary endpoints: relationship between all-cause readmission and one-year all-cause mortality in the derivation LEDA and validation BASEL V cohorts.
Figure S3. Patient flowchart of the validation BASEL V cohort.

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