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ORIGINAL ARTICLE

Impact of heart failure on all-cause mortality in COVID-19: findings from the Eurasian International Registry

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Abstract

Aims To study all-cause mortality in patients hospitalized with COVID-19 with or without chronic heart failure (CHF) during hospitalization and at 3 and 6 months of follow-up.

Methods and results The international registry Analysis of Comorbid Disease Dynamics in Patients with SARS-CoV-2 Infection (ACTIV) was conducted at 26 centres in seven countries: Armenia, Belarus, Kazakhstan, Kyrgyzstan, Moldova, Russian Federation, and Uzbekistan. The primary endpoints were in-hospital all-cause mortality and all-cause mortality at 3 and 6 months of follow-up.

Of the 5616 patients hospitalized with COVID-19, 917 (16.3%) had CHF. Total in-hospital mortality was 7.6%. In-hospital mortality was higher in patients with CHF than in patients without a history of CHF [17.7% vs. 4.0%, $P < 0.001$; odds ratio (OR) 4.614, 95% confidence interval (CI) 3.633–5.859; $P < 0.001$]. The risk of in-hospital all-cause mortality correlated significantly with the severity of CHF; specifically, the risk of in-hospital all-cause mortality was greater for patients in New York Heart Association functional classes III and IV (OR 6.124, 95% CI 4.538–8.266; $P < 0.001$ vs. patients without CHF) than for patients in functional classes I and II (OR 2.446, 95% CI 1.831–3.267, $P < 0.001$ vs. patients without CHF). The risk of mortality in patients with ischemic CHF was 58% higher than in patients with non-ischaemic CHF [OR 1.58 (95% CI 1.05–2.45), $P = 0.030$]. In the first 3 months of follow-up, the all-cause mortality rate in patients with CHF was 10.32%, compared with 1.83% in patients without CHF ($P < 0.001$). At 6 months of follow-up, NYHA classes II–IV was a strong risk factor for all-cause mortality [OR 5.343 (95% CI 2.717–10.508); $P < 0.001$].

Conclusions Hospitalized COVID-19 patients with CHF have an increased risk of in-hospital all-cause mortality, which remains high 6 months after discharge.

Keywords Coronavirus disease 2019; Cardiovascular disease; Chronic heart failure; SARS-CoV-2

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Introduction

Coronavirus disease 2019 (COVID-19), a new coronavirus infection caused by the SARS-COV-2 virus, resulted in a rapidly spreading worldwide pandemic associated with very considerable morbidity and mortality for more than 2 years. The association between cardiovascular diseases (CVD) and a negative prognosis in COVID-19 is well established.[1] However, there have been limited data on the prevalence and prognostic significance of chronic heart failure (CHF) in a population of patients with COVID-19 in the acute period of infection, nor of the course of CHF in the post-discharge period after COVID-19-related hospitalization.

In the Eurasian region (total population >200 million people), there were no clinical registries to collect and analyse information on the interplay between COVID-19 and co-morbid

conditions. To address this deficit, the international registry Analysis of Comorbid Disease Dynamics in Patients with SARS-CoV-2 Infection (ACTIV)[2] was established. We now report our findings on the effect of CHF on all-cause mortality in patients enrolled in the ACTIV registry.

Methods

A detailed description of the study design and statistical data processing methods has been published previously.[3] Further information about the ACTIV registry is available on the website of the Eurasian Association of Therapists or via a direct link (https://ACTIV.euat.ru).

The registry is organized and overseen by three committees: an organizational committee, a supervisory committee, and a committee for endpoint analysis and control of completion of individual registration cards (IRCs). IRCs and document turnover were in electronic format only.

Healthcare professionals from seven Euroasian countries participated in the ACTIV registry: Armenia (one centre), Belarus (one centre), Kazakhstan (one centre), Kyrgyzstan (one centre), Moldova (one centre), Russian Federation (20 centres), and Uzbekistan (one centre).

Study population

The registry included hospitalized men and women aged ≥18 years with a confirmed diagnosis of COVID-19 [positive result by polymerase chain reaction testing of a nasopharyngeal sample, a positive blood antigen test, typical computerized tomography (CT) image]. Exclusion criteria for the registry were age ≤18 years at hospitalization and outpatients.

Enrolled patients were divided into two cohorts according to their CHF status:

i Patients with a history of CHF, including heart failure (HF) with preserved ejection fraction (EF), mildly reduced EF, or reduced EF. The diagnosis of HF was based on the national clinical guidelines of each participating country.
ii Patients without a history of CHF.

Study procedures

Demographic data (age, sex, and ethnicity), clinical data (medical history, medications taken at admission, cardiac manifestations of COVID-19 at admission, signs and symptoms of COVID-19 at admission, and physical examination at admission), laboratory findings, chest X-ray and/or CT scan data, electrocardiographic and echocardiographic data, and data on clinical course in hospital and COVID-19 complications were extracted from electronic medical records using a standardized data collection form on three visits: Visit 1 (day of admission); Visit 2 (7 days after admission); and Visit 3 (day of discharge).

Further data on the post-discharge status of patients were obtained via telephone interviews using a standardized questionnaire at 3 and 6 months after recovery from COVID-19. Telephone calls were planned only for the patients who gave their consent at discharge to take part in the procedure. The questionnaire for interviewing patients by telephone is available at https://activ.euat.ru/documents.

Data acquisition, pooling, and standardization

Patient recruitment commenced on 29 June 2020 and ended on 29 October 2020. Data were collected from 26 health centres in the seven participating countries. A total of 188 physicians took part in the registry. Details on medical contributors are provided in Appendix S1, along with details of members of the Data Monitoring and the Endpoint Committees.

Inclusion of patients was limited by the number of COVID-19 cases and local COVID-19 triage rules. Whenever centres provided a set of eligible patients, we attempted to obtain consecutive patients. Each IRC was checked by reviewers operating as part of the central structure of the registry. The medical diagnosis was established on the basis of ICD-10 criteria.

We developed a standardized data collection form to control for the fact that definitions of clinical manifestations may vary from country to country and from centre to centre. Registry documentation was maintained in Russian.

Pseudo-anonymized forms (with protected keys stored at the local centres) were collected by the core working group and merged into a common database, and a common identifier was created for each patient.

Data quality was checked for all variables. For categorical variables, numbers that did not correspond to any of the predefined categories were excluded. For continuous variables, temporal variables (expressed in number of days) were excluded as follows: negative values (<0 days) and values >365 days.

Data quality for continuous variables was further checked by systematically estimating the mean, median, minimum, maximum, and range of values for each centre and comparing them with the total values for the entire registry. We identified outliers and implausible values and, if necessary, questioned participants to address any issues that arose.

Laboratory measurements

Laboratory parameters comprised erythrocytes, haemoglobin, white blood cells (lymphocytes and neutrophils), platelets, high-sensitivity cardiac troponin T or I,

C-reactive protein (CRP), procalcitonin, arterial blood gases (partial pressures of CO_2 and O_2), aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, glucose, albumin, creatinine (for use in Cockroft–Gault estimates), serum potassium and sodium levels, D-dimer, ferritin, international normalized ratio, and fibrinogen.

Endpoints

The primary endpoints were in-hospital all-cause mortality and all-cause mortality within 6 months after hospital discharge.

Statistical analysis

The registry data were processed using the IBM SPSS Statistics 25 statistical package. Categorical variables are represented as numbers of patients, with percentages in parentheses. Continuous variables are described as medians with lower and upper quartiles. Intergroup differences were tested using Student's *t*-test for normally distributed data and the Mann–Whitney *U* test for non-normally distributed data. Proportions were compared using the χ^2 test or Fisher's exact test where appropriate. Logistic regression (univariate regression followed by multivariate stepwise regression) identified variables that most significantly influenced mortality and the need for hospital admission. Correlation matrices and multi-input frequency tables were constructed to avoid multi-collinearity and incorrect interpretation of relationships.

Ethics

The study was conducted in accordance with the provisions of the Declaration of Helsinki, approved by the Ethics Committee of the Federal State Autonomous Educational Institution of Higher Education 'Pirogov Russian National Research Medical University' of the Ministry of Healthcare of the Russian Federation, and registered in the ClinicalTrials.gov database as Analysis of Chronic Non-infectious Diseases Dynamics After COVID-19 Infection in Adult Patients (ACTIV) (identifier NCT04492384).

Informed consent was obtained from all patients for the use of clinical, laboratory, and instrumental data from medical documentation in the IRCs on condition of anonymity, as well as for receipt of telephone calls 3 and 6 months after discharge. Further information on the principles and practical aspects of informed consent in the ACTIV registry is available at https://activ.euat.ru/documents (in Russian only).

Results

The registry included 5616 hospitalized patients with laboratory-confirmed COVID-19. The average hospital stay was 14 ± 4.5 days [median 14.0 days, interquartile range (IQR) 11.0;17.0]. *Table 1* shows baseline characteristics of COVID-19 patients with and without pre-existing CHF. A total of 917 (16.3%) patients in the ACTIV registry had incident CHF. Of those patients, 10.6% were in New York Heart Association (NYHA) functional classes I and II, and 5.6% were in NYHA classes III and IV. The number of patients with non-ischaemic CHF was 264 (28.8%), and the number of patients with ischaemic CHF was 653 (71.2%).

Patients with left ventricular EF $\leq$ 40%, 41–49%, and $\geq$50% accounted for 9.78%, 30.33%, and 59.89% of the total cohort, respectively.

Patients with CHF were characterized by a higher level of co-morbidity and greater abnormalities in laboratory and instrumental markers of the severity of COVID-19 than patients who did not have CHF. Patients with CHF also differed from those without CHF with regard to the incidence of acute infectious complications. For example, deep vein thrombosis (DVT), strokes, bacterial pneumonia, acute respiratory distress syndrome (ARDS), cytokine storm, acute kidney injury (AKI), and sepsis were more frequent in patients with CHF.

Patients with CHF were, on average, older than those without CHF [median 69 (IQR 63–79) vs. 56 (45–65) years, $P < 0.001$]. For this reason, further comparison was made using logistic regression after controlling for age.

The overall in-hospital all-cause mortality rate was 7.6%. Patients with CHF had significantly higher all-cause mortality than those without CHF (17.7% vs. 4.0%, $P < 0.001$).

The presence of CHF correlated strongly with in-hospital all-cause mortality risk [odds ratio (OR) 4.614, 95% confidence interval (CI) 3.633–5.859, $P < 0.001$]. The risk of death was related to the severity of CHF and was greater for patients with NYHA class III–IV CHF (OR 6.124, 95% CI 4.538–8.266, $P < 0.001$) than those with NYHA class I–II CHF (OR 2.446, 95% CI 1.831–3.267, $P < 0.001$). CHF was a recurring feature of disease clusters associated with increased mortality risk, including CHF + arterial hypertension (AH) (OR 3.963, 95% CI 3.022–5.197); CHF + AH + coronary heart disease (CHD) (OR 4.082, 95% CI 3.054–5.455); and CHF + AH + CHD + type 2 diabetes mellitus (OR 4.215, 95% CI 2.784–6.382) ($P < 0.001$ for all comparisons with patients who did not have the respective disease cluster).

Information on demographic, clinical-instrumental, and laboratory characteristics was available for 681 surviving and 146 deceased patients with CHF (*Table 2*). Comparison of mortality rates between the ischemic CHF and non-ischaemic CHF groups showed that 114 patients died in the ischaemic CHF group (78.1% of all deaths) and 32 died in the non-ischaemic CHF group (21.9% of all deaths). Mortality risk was 58% higher in patients with ischemic CHF [OR

Table 1 Comparative baseline characteristics of COVID-19 patients with and without CHF

	Total cohort $N = 5616$	HF subgroup $n = 917$	Non-HF subgroup $n = 4699$	P age-adjusted -
Age (years); median (IQR)	58 [48–68]	69 [63–79]	56 [45–65]	0.001
Men, *n* (%)	2561 (45.6)	444 (48.4)	2119 (45.1)	0.001
Died, *n* (%)	348 (6.2)	161 (17.7)	187 (4.0)	0.001
CT 3–4, *n* (%)	1100 (19.6)	253 (27.4)	847 (18.0)	0.001
SpO_2 75–94%, *n* (%)	2302 (41.0)	568 (62.0)	1734 (36.9)	0.001
$SpO_2 < 75\%$, *n* (%)	72 (1.3)	38 (4.1)	34 (0.7)	0.001
Glucose ≥7 mmol/L in patients with diabetes mellitus, *n* (%)	711/984 (72.3)	228/298 (76.5)	483/686 (70.5)	0.04
Arterial hypertension, *n* (%)	3111 (55.4)	809 (88.1)	2302 (49.0)	0.001
Obesity (body mass index ≥30 kg/m2), *n* (%)	1952 (34.8)	367 (39.9)	1585 (33.7)	0.001
Coronary heart disease, *n* (%)	1156 (20.6)	653 (71.2)	503 (10.7)	0.001
Previous myocardial infarction, *n* (%)	321 (5.7)	213 (23.2)	108 (2.3)	0.001
Stroke, *n* (%)	240 (4.3)	107 (11.7)	133 (2.8)	0.001
Diabetes mellitus type 2, *n* (%)	984 (17.5)	298 (32.6)	686 (14.6)	0.001
Atrial fibrillation, *n* (%)	383 (6.8)	242 (26.4)	141 (3.0)	0.001
Chronic kidney disease, *n* (%)	422 (7.5)	188 (20.6)	234 (5.0)	0.001
COPD, *n* (%)	259 (4.6)	99 (10.8)	160 (3.4)	0.001
Anaemia, *n* (%)	1504 (26.8)	369 (40.1)	1135 (24.1)	0.001
SpO_2(%); median [IQR]	95 [93–97]	93 [90–95]	95 [93–97]	0.001
Haemoglobin (g/L); median [IQR]	130 [118–141]	125 [111–136]	131 [120–142]	0.001
Leukocytes ($\times 10^9$/L); median [IQR]	7 [5.4–9.72]	8.3 [6.1–11.7]	6.9 [5.3–9.2]	0.001
Lymphocytes (%);median [IQR]	18.8 [10–28]	14.55 [7.4–21.9]	20 [10.3–29.4]	0.001
C-reactive protein (mg/L); median [IQR]	34.3 [12–90]	45.05 [18.1–102.0]	31.1 [10.61–86.0]	0.001
D-dimer (μg FEU/mL); median [IQR]	0.77 [0.35–1.81]	1.1 [0.35–2.18]	0.74 [0.35–1.61]	0.04
Glomerular filtration rate (mL/min/1.73 m^2); median [IQR]	70.07 [54.46–86.51]	56.26 [39.84–73.95]	72.55 [58.19–89.09]	0.001
Alanine aminotransferase (units/L); median [IQR]	34 [24.0–52.0]	37 [25.3–55.0]	34 [23.5–51.0]	0.001
Alanine aminotransferase (units/L); median [IQR]	33 [21.0–58.4]	31.65 [20.0–51.0]	33.5 [21.0–59.0]	0.02
Glucose in non-diabetic patients (mmol/L); median [IQR]	5.6 [5.0–6.5]	5.98 [5.0–7.0]	5.6 [5.0–6.5]	0.001
Procalcitonin (ng/mL); median [IQR]	0.16 [0.06–0.40]	0.21 [0.11–0.50]	0.13 [0.05–0.36]	0.001
Troponin I (ng/mL); median [IQR]	0.03 [0.0–0.1]	0.08 [0.02–0.13]	0.01 [0.00–0.06]	0.001
Complications				
Deep vein thrombosis, *n* (%)	23 (0.4)	10 (1.1)	13 (0.3)	0.03
Pulmonary embolism, *n* (%)	34 (0.6)	14 (1.5)	20 (0.4)	0.12
Stroke, *n* (%)	26 (0.5)	13 (1.3)	13 (0.3)	0.22
Bacterial pneumonia, *n* (%)	552 (9.8)	183 (20.1)	369 (7.9)	0.001
ARDS, *n* (%)	331 (5.9)	148 (16.2)	183 (3.9)	0.001
Cytokine storm, *n* (%)	1306 (23.3)	294 (31.8)	1012 (21.5)	0.001
Acute kidney injury, *n* (%)	490 (8.7)	152 (16.6)	338 (7.2)	0.001
Myocarditis, *n* (%)	17 (0.3)	4 (0.4)	13 (0.3)	0.63
Sepsis, *n* (%)	17 (0.3)	10 (1.1)	7 (0.1)	0.01

ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; CT, computerized tomography; CT 4, 75–100% lesion; CT 3, 50–75% lesion; FEU, fibrinogen equivalent units; IQR, interquartile range; SpO_2, saturated partial pressure of oxygen.

Table 2 Comparison of characteristics of patients in the ACTIV registry with COVID-19 plus CHF according to survival status

	Patients who survived *n* = 681	Patients who died *n* = 146	*P* for differences -	Odds ratio (95% confidence interval)
Age (years), median [IQR]	68 [62–76]	77 [66–83]	0.001	-
Men, *n* (%)	322 (47.4)	77 (52.7)	0.24	1.237 (0.865–1.769)
Men aged ≥60 years, *n* (%)	254 (37.3)	68 (46.9)	0.03	1.483 (1.034–2.129)
Computerized tomography Grade 1 (0–25% lung lesion) or Grade 2 (26–50% lung lesion), *n* (%)	512 (75.1)	86 (58.9)	0.001	2.105 (1.372–3.228)
Computerized tomography Grade 3 (51–75% lung lesion) or Grade 4 (76–100% lung lesion), *n* (%)	169 (24.9)	60 (41.1)		
C-reactive protein >40 mg/L, *n* (%)	341 (50.1)	92 (63.1)	0.01	1.701 (1.117–2.590)
Glucose ≥7 mmol/L in non-diabetic patients, *n* (%)	114/467 (24.4)	37/83 (45.1)	0.001	2.545 (1.513–4.281)
Glucose ≥ 7 mmol/L in patients with diabetes, *n* (%)	157/214 (73.2)	53/63 (84.1%)	0.08	1.998 (0.916–4.357)
Arterial hypertension and aged ≥60 years, *n* (%)	495 (72.7)	126 (86.2)	0.01	2.345 (1.421–3.872)
Obesity and aged ≥60 years, *n* (%)	187 (27.5)	58 (39.7)	0.01	1.732 (1.114–2.621)
Coronary artery disease, *n* (%)	471 (69.2)	114 (78.1)	0.03	1.588 (1.039–2.428)
Coronary artery disease and aged ≥60 years, *n* (%)	411 (60.3)	107 (73.1)	0.001	1.788 (1.201–2.661)
Stroke, *n* (%)	65 (9.5)	33 (22.6)	0.001	2.768 (1.739–4.404)
Type 2 diabetes mellitus, *n* (%)	214 (31.4)	63 (43.2)	0.01	1.656 (1.150–2.387)
Type 2 diabetes mellitus and aged ≥60 years, *n* (%)	173 (25.4)	57 (39.3)	0.001	1.906 (1.309–2.774)
Atrial fibrillation, *n* (%)	163 (23.9)	57 (39.0)	0.001	2.035 (1.397–2.695)
Atrial fibrillation and aged ≥60 years, *n* (%)	144 (21.1)	53 (36.6)	0.001	2.155 (1.466–3.168)
Chronic kidney disease, *n* (%)	121 (17.8)	45 (30.8)	0.001	2.062 (1.379–3.084)
Chronic kidney disease and aged ≥60 years, *n* (%)	102 (15.0)	39 (26.9)	0.001	2.078 (1.361–3.172)

Medians and interquartile ranges reported for quantitative variables; proportion of categories reported for categorical variables. Results are presented as *n* (%) or as median with interquartile range (IQR). Comparisons based on Mann–Whitney or $\chi 2$ tests.

1.58 (95% CI 1.05–2.45), *P* = 0.030]. Inspections within the CHF subgroup based on survival status established that deceased patients were older and that the combination of male sex and age ≥60 years was associated with a markedly increased risk of all-cause mortality (*Table 2*). Other risk markers for all-cause mortality in this subgroup were severity of lung injury on CT scan, CRP > 40 mg/L, and glucose ≥7 mmol/L in patients without diabetes mellitus (*Table 2*).

Demographic features associated with increased all-cause mortality included the combination of age ≥60 years plus AH or obesity. Factors most strongly associated with increased all-cause mortality risk in patients with CHF were (in descending order) history of stroke, glucose ≥7 mmol/L in patients without diabetes, advanced (Grade 3–4) CT evidence of lung damage, chronic kidney disease (CKD), atrial fibrillation (AF), CRP > 40 mg/L, type 2 diabetes mellitus, and CHD.

A comparative analysis of the severity of laboratory markers of infection in deceased and surviving patients with CHF demonstrated that patients who died had lower saturated partial oxygen pressure (SpO_2), partial oxygen pressure (pO_2), haemoglobin, lymphocytes, platelets and glomerular filtration rate (GFR) (*Table S1*). Compared with surviving patients in the CHF subgroup, those who died also had higher white blood cell count, CRP, D-dimer, AST, blood glucose levels (regardless of diabetes status), and procalcitonin level.

Examination of pre-admission therapies relevant to the management of CHF established that 45% of the CHF subgroup patients were taking angiotensin-converting enzyme inhibitors (ACEIs) and 23.1% were taking angiotensin receptor blockers (ARBs); beta-blockers (BBs) were prescribed to 63.4% of patients, mineralocorticoid receptor antagonists (MRAs) to 4.0% of patients (but 12.6% of HF patients with left ventricular EF < 40%), and diuretics to 54.5% of patients. None of the included patients was reported to be taking sacubitril/valsartan or SGLT2 inhibitors, and only nine were taking eplerenone. A comparison of dead and surviving patients with CHF demonstrated that prior use of BBs, statins, oral antiplatelet drugs, and oral antihyperglycemic medications was associated with a reduction in all-cause mortality (*Table 3*). A non-significant trend (*P* = 0.054) was identified for a reduced risk of death in patients prescribed ACEI therapy. Prior MRA treatment was associated with a non-significant trend for increased risk of all-cause mortality [OR 2.342 (95% CI 0.921–4.543), *P* = 0.07] (*Table 3*).

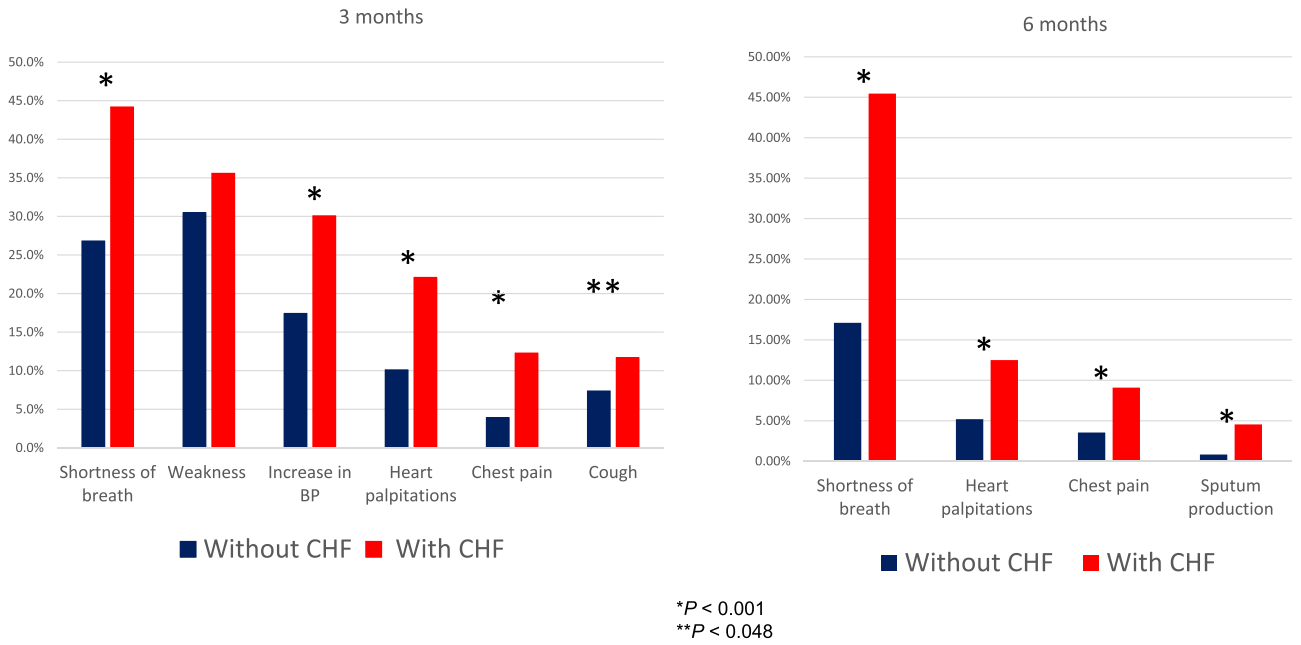
Post-discharge status of COVID-19 patients with CHF

For follow-up data, 3007 patients were contacted by telephone 3 months after discharge from hospital and 2011 patients after 6 months. At 3 months, 432 patients (14.4%) did not respond to the follow-up call, and 390 responses (12.9%) were considered incomplete. At 6 months, 409 patients (20.3%) did not respond to the follow-up call, and there

Table 3 Characteristics of survivors and deceased patients with CHF in the ACTIV registry according to therapy preceding hospital admission

Background therapy	Overall cohort $n = 827$	Patients who survived $n = 681$	Patients who died $n = 146$	P for differences -	Odds ratio (95% confidence interval) -
Angiotensin-converting enzyme inhibitors, *n* (%)	372 (45.0)	317 (46.5)	55 (37.5)	0.054	0.689 (0.471–1.007)
Angiotensin blockers, *n* (%)	191 (23.1)	163 (24.0)	28 (19.1)	0.22	0.75 (0.472–1.193)
Beta blockers, *n* (%)	524 (63.4)	455 (66.8)	69 (47.1)	0.001	0.441 (0.304–0.642)
Mineralocorticoid receptor antagonists, *n* (%)	37 (4.6)	23 (3.4)	14 (9.6)	0.07	2.342 (0.921–4. 543)
Statins, *n* (%)	341 (41.2)	299 (43.9)	42 (27.9)	0.001	0.495 (0.330–0.742)
Ticagrelor, clopidogrel, prasugrel, *n* (%)	101 (12.2)	91 (13.4)	10 (6.6)	0.03	0.459 (0.225–0.937)
Oral antidiabetic therapy for type 2 diabetes mellitus, *n* (%)	260 (31.2)	231 (34.3)	29 (20.3)	0.04	0.489 (0.244–0.981)

Figure 1 Comparative analysis of symptomatology in COVID-19 patients in the ACTIV registry with or without CHF (NYHA classes II–IV) at 3 and 6 months of follow-up. BP, blood pressure. *$P < 0.001$. **$P < 0.048$.



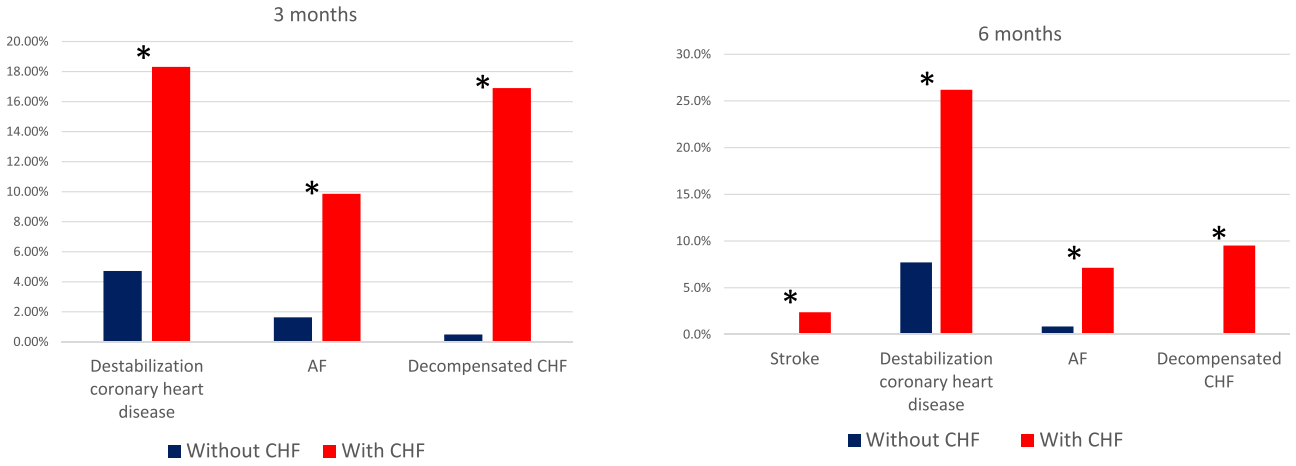
were 394 (19.7%) incomplete responses. Analysis was thus based on data from 2185 telephone interviews at 3 months (including 174 patients who answered the telephone but refused to continue collaboration) and 1208 interviews at 6 months.

In the general cohort of ACTIV patients, deterioration of at least one symptom or appearance of at least one new symptom occurred in 38.2% of patients during the first 3 months of follow-up and in 27.7% after 6 months of follow-up. Patients with CHF were more likely than patients without CHF to have a new symptom or deterioration of symptoms that were typical for them before COVID-19 (*Figure 1*). Dyspnoea markedly worse than before index hospitalization was recorded during the first 3 months post-discharge in 44.17% of patients with CHF and 26.8% of patients without CHF ($P < 0.0001$) and in 45.45% of patients with CHF and 17.11% without CHF at 4–6 months post-discharge ($P < 0.0001$).

Another widespread finding in patients with CHF was AH no longer controlled by standard-of-care therapies. This was observed more frequently in patients with CHF than in those without CHF in the first 3 months post-discharge (30.06% vs. 17.41%, $P < 0.0001$) (*Figure 1*). Patients with CHF were also significantly more likely than those without CHF to have palpitations, chest pain, and cough (in descending order of frequency) in the first 3 months post-discharge and to have palpitations, chest pain, and sputum production at 4–6 months (*Figure 1*).

Almost one-third (29.2%) of the total ACTIV population sought unplanned medical care in the post-hospital period,

Figure 2 Comparative analysis of the frequency and causes of healthcare seeking in COVID-19 patients in the ACTIV registry with or without CHF (NYHA classes II–IV) at 3 and 6 months of follow-up. AF, atrial fibrillation. *$P < 0.001$.



and at least twice during the first 3 months. Patients with CHF were significantly more likely than those without CHF to seek unplanned care in the first 3 months for (in decreasing frequency) CHD worsening, decompensation of CHF, and onset of AF and at 4–6 months for (in decreasing frequency) CHD worsening, decompensation of CHF, AF, and stroke (*Figure 2*).

Newly diagnosed diseases in the general ACTIV patient population were reported in 5.6% and 6.4% of patients in the post-hospital period at 3 and 6 months, respectively. These included AH (3%), CHD (1.4%), type 2 diabetes mellitus (1.4%), AF (0.3%), and arthritis (0.3%). Patients with CHF were more likely than those without CHF to have a first diagnosis (in descending order of frequency) of AF, COPD, stroke, DVT, or CHD in the initial 3 months post-discharge, and, in the period 4–6 months post-discharge, patients with CHF were more likely to experience stroke (*Table S2*).

All-cause mortality in the general population of the ACTIV registry in the post-hospital period was 1.9% during the first 3 months of follow-up and 0.2% during months 4–6 of follow-up. CHF severity corresponding to NYHA classes II–IV was found to be a strong predictor of all-cause mortality in the post-hospital period (OR 5.343, 95% CI 2.717–10.508, $P < 0.001$). The highest rate of all-cause mortality was observed in the first 3 months in the group of patients with NYHA class II–IV CHF (10.32%); the corresponding rate in patients without CHF was 1.83% (*Figure S1*). Cardiovascular complications (38.46%) were prominent among all causes of death in the post-hospital period in patients with CHF: acute decompensation of CHF (23.08%) was the single most common cause of death, with additional contributions from acute MI and stroke (7.69% each).

Discussion

The main findings of our study suggest that pre-existing CHF in hospitalized patients with COVID-19 was associated with high all-cause mortality and more frequent complications both in hospital and after discharge from the hospital. To our knowledge, this is the first registry investigating the interplay between COVID-19 and pre-existing morbidities, which has included patients with CHF in the Eurasian region. Some comparison with other studies is therefore instructive.

In a Cochrane systematic review, Pellicori *et al.*[1] examined the interplay between COVID-19, cardiovascular co-morbidities, and cardiovascular complications. It should be noted that almost 90% of the studies included in that meta-analysis were of a retrospective nature. Among the 20 prospective investigations identified, only the study by Petrilli *et al.*[4] recruited a patient population similar in size to that of ACTIV (n = 5279 vs. n = 5616) and did so in a single centre in New York.

The average incidence of CHF in patients with COVID-19 in the Cochrane meta-analysis averaged 6.5%[1] but ranged from 0% to 28%. Substantial variation in incidence of CHF has been recorded: for example, Petrilli *et al.*[4] reported a CHF incidence of 7% in patients with COVID-19; a retrospective analysis by Alvarez-Garcia *et al.*[5] (n = 6439) reported a 6.6% prev-

alence of CHF among hospitalized patients with COVID-19; and Palmieri *et al*. in Italy[6] reported an incidence of 16% in patients with COVID-19. Our own finding of a CHF incidence of 16.3% in patients hospitalized with COVID-19 is thus towards the upper end of the range established in other research. This may reflect particular demographic features of our population that we have not yet explored.

In our study, patients with CHF were on average 13 years older than the comparator subgroup and exhibited more co-morbidities. Our CHF cohort exhibited a high prevalence of hypertension, CVD or cerebrovascular disease, and type 2 diabetes mellitus, much in accordance with the aggregate findings of Pellicori *et al*.[1] and Petrilli *et al*.[4] In contrast to these two studies, we did not identify a marked prevalence of obesity in our CHF patients compared with the non-CHF subgroup, but obesity was a risk marker for worse outcomes in our CHF patients, a finding in line with general experience with COVID-19.[7–9]

Our patients with CHF experienced a more severe course of COVID-19 and more frequent complications in the acute period of infection than the non-CHF comparators. These findings are consistent with those from a range of other studies.[5,10–14]

Mortality among our patients with CHF was four times higher that than in those without CHF (17.7%vs. 4.0%, $P < 0.001$). Similarly, other authors have reported higher mortality in patients with COVID-19 and CHF compared with those without CHF.[4,10,11]

The major factors associated with increased mortality risk in ACTIV patients with CHF were NYHA class (more severe CHF conferred greater risk); laboratory and instrumental markers of severe infection; and the following co-morbidities (in descending order of their influence on mortality risk): history of stroke, CKD, AF, type 2 diabetes mellitus, and CHD. Age ≥60 years had a consistently strong adverse influence on prognosis, and there was a notable association between age ≥60 years and male sex. These findings are compatible with those in various other reports, including those of Saleh *et al*.,[15] Alvarez-Garcia *et al*.,[16] the SEMI-COVID-19 registry[17] (which included 1718 patients and reported an overall mortality rate of 47.6%), and Belarte-Tornero *et al*.[11] Also of note is the study by Bhatt *et al*.,[18] whose retrospective analysis of 8383 HF patients hospitalized with COVID-19 identified male sex, morbid obesity, and greater age as being associated with higher risk of mortality. Mortality in that database analysis of patients with HF plus COVID-19 approached 25%, a value even higher than that in our registry. This may reflect growing experience in the management of COVID-19 in the second and third quarters of 2020, a possibility identified by the authors of that investigation.

Based on the ACTIV registry data, deceased patients with or without diabetes mellitus tended to have higher blood glucose levels than patients who survived. This finding is consistent with the findings of the study by Long *et al*.,[19] which showed that both diabetes mellitus and hyperglycaemia without diabetes mellitus were independently associated with adverse outcomes of COVID-19 with risk coefficients of 10.41 and 3.58, respectively. Elsewhere, Wang *et al*. have reported that a plasma glucose level ≥7.0 mmol/L at hospitalization is an independent predictor of 28-day mortality in patients with COVID-19 without a prior diagnosis of diabetes mellitus.[20] This phenomenon may have a number of explanations. For example, patients with COVID-19 may suffer from stress-induced hyperglycaemia.[21] Patients in a critical condition may develop acute insulin resistance, which manifests as hyperglycaemia and hyperinsulinaemia.[22] Separately or perhaps simultaneously, drugs such as antibiotics and corticosteroids can also increase serum glucose levels.[23,24]

Continuation of guideline-directed medical therapy in chronic CHF patients is considered of primary importance for effective management in the era of COVID-19.[25] In-hospital withdrawal of drug therapy, including ACEIs, ARBs, BBs, and MRAs, is associated with higher mortality in acute decompensated heart failure.[10] Only 12.6% of CHF patients included in the ACTIV registry were pre-treated with MRAs, and none of the included patients was reported to take sacubitril/valsartan or SGLT2 inhibitors. Notwithstanding differences in the registration of the above-mentioned medications in each country participating in the registry, we believe that it is necessary to make additional efforts to optimize the drug management of patients with CHF and COVID-19 in the Eurasian region. In our study, pre-treatment of patients with CHF and COVID-19 with statins, oral antiplatelet, and anti-hyperglycaemic medications was associated with a reduction in mortality. Identification of reasons for this are outside the scope of the present report, but we speculate that prescription of several of these classes of drugs might be considered as a part of medical therapy for CHF patients who develop COVID-19. Further investigation of these possibilities may be instructive for the medical management of COVID-19 in patients with CHF.

Throughout the post-discharge period, patients with CHF were more likely than CHF-free patients to experience (in descending order of frequency) breathlessness, weakness, uncontrolled hypertension, palpitations, cough, and chest pain. Patients with CHF were also significantly more likely to seek unscheduled care in the first 3 months for (in descending order of frequency) deterioration of ischaemic heart disease and decompensation of CHF and AF and, during months 4–6 post-discharge, for those three complications plus stroke. The scope and prospective nature of the ACTIV registry make it one of the first large reports on the post-discharge status of COVID-19 patients with CHF.

According to our data, 5.6% and 6.4% of patients in the ACTIV registry population were diagnosed with a ‘new’ disease, including ‘new’ CHF, in the post-discharge period during 3 and 6 months of follow-up, respectively. A number of other

reports also point to the possibility of 'new' HF, in both the acute and post-hospitalization periods of COVID-19.[16,26] Signs of myocardial inflammation and fibrosis on magnetic resonance images have been reported in patients discharged from hospital, and these may persist for several months after discharge.[27–29] The significance of these signs of cardiac involvement is not fully known, but one evident possibility is that the SARS-COV-2 infection may be a risk factor for the development of CHF, either by direct myocardial effects or the propagation of AF or the destabilization of recognized co-morbidity risk factors such as AH, kidney disease, or diabetes. This may extend also to HF with preserved ejection fraction.[30,31]

The mortality rate during the first 3 months after discharge in patients with NYHA class II–IV CHF was 10.32%, making CHF functional class one of the strongest identifiers (and, we suppose, determinants) of fatal outcome in the early post-hospitalization period. Cardiovascular events (acute CHF, acute MI, and stroke) were recorded causes of death in 38.5% of cases. A high rate of post-discharge mortality, especially in patients with CVD, has been reported by various authors.[32–35]

Viral infections are known to be a potential cause of decompensation of CHF.[36,37] That general premise is affirmed for the specific situation of SARS-CoV-2 by the new data from the ACTIV registry: CHF had a negative impact on the prognosis of patients with COVID-19, increasing the risk of death in both the acute and post-hospitalization periods. COVID-19, in turn, increased the risk of decompensation of existing CHF and the development of new HF. Various other recent publications have either corroborated the effect of this detrimental relationship between COVID-19 and CHF on patient prognosis or outlined some possible mechanistic explanations for these adverse effects.[38–41] The negative correlation between COVID-19 and CHF needs to be taken into account when deciding whether to prioritize hospital admission for patients with a history of CHF.

Limitations of the study

Although the ACTIV registry nominally included all patients who were admitted to hospital with a diagnosis of COVID-19 during the registry timeline, the potential for selection bias must be acknowledged. As with other multicentre registries, there were practical limits to our ability to verify data for every patient. Echocardiography was performed in the context of routine clinical practice, the assessment of left ventricular EF was not standardized, and the information on the levels natriuretic peptides was not available in many patients. Taken together, these factors may have led to misclassification of some patients, and this needs to be considered when interpreting the data. As regards mortality rates and post-discharge complications, our findings may have been influenced by differences in the management of patients with CHF in the different participating countries.

Deteriorating patient condition, whether due to progression of CHF, late complications of COVID-19, the combination of both conditions, or other illnesses, may have created a selection bias in our follow-up cohort by excluding the most severely affected participants. The implication of such a bias could be that outcomes in the whole ACTIV CHF cohort were even worse than revealed by our investigations.

Conclusions

ACTIV is currently the only registry that generates data on the COVID-19 patient population in the Eurasian region and the course of COVID-19 and co-morbid disease dynamics over a 6-month post-discharge period. Our findings show that CHF appears to be encountered more often in COVID-19 patients in the Eurasian region than in some other countries and territories. Advanced CHF (NYHA classes III and IV) is the strongest risk predictor of fatal outcome for COVID-19, and its negative impact on prognosis extends into the early post-hospitalization period, when COVID-19 patients with CHF feel worse than those without it, are more likely to seek unplanned medical care, and are more likely to develop *de novo* disease. This suggests the need to develop optimal rehabilitation regimens and a multidisciplinary approach to the management of patients with CHF following COVID-19 infection.

This detrimental interplay of CHF and COVID-19 requires careful monitoring, as there is a high likelihood of an increased burden of CHF and a change in the course of this condition due to COVID-19 infection. Patients with CHF should be a priority group in national or population-wide vaccination programmes. Further analysis of the ACTIV database and similar resources may help to guide the medical response to this continuing challenge.

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Conflict of interest

The authors and investigators declare no conflicts of interest in respect of their work on the ACTIV registry.

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The Eurasian Association of Therapists (EAT) bore all the costs of the ACTIV registry. The EAT is an independent association that provides opportunities for its members to share experience and discuss problems of evidence-based medicine and clinical practice.

Supporting information

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

Appendix S1. Supporting information.

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