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ORIGINAL ARTICLE

Effects of the COVID-19 pandemic on heart failure hospitalizations in Japan: interrupted time series analysis

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Abstract

Aims The Coronavirus Disease 2019 (COVID-19) pandemic has had unprecedented effects on health care utilization for acute cardiovascular diseases. Although hospitalizations for acute coronary syndrome decreased during the COVID-19 pandemic, there is a paucity of data on the trends and management of heart failure (HF) cases. Furthermore, concerns have been raised that angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) may increase susceptibility to COVID-19. This study aimed to elucidate changes in HF hospitalizations from the COVID-19 state of emergency in Japan and investigated changes in the prescription of ACEIs and ARBs, and in-hospital mortality.

Methods and results We performed an interrupted time series analysis of HF hospitalizations in Japan to verify the impacts of the COVID-19 state of emergency. Changes in the weekly volume of HF hospitalizations were taken as the primary outcome measure. Between 1 April 2018 and 4 July 2020, 109 429 HF cases required admission. After the state of emergency, an immediate decrease was observed in HF cases per week [−3.6%; 95% confidence interval (CI): −0.3% to −6.7%, $P = 0.03$]. There was no significant change in the prescription of ACEIs or ARBs after the state of emergency (4.2%; 95% CI: −0.3% to 8.9%, $P = 0.07$). The COVID-19 pandemic had no effect on in-hospital mortality among HF patients (5.3%; 95% CI: −4.9% to 16.6%, $P = 0.32$).

Conclusions We demonstrated a decline in HF hospitalizations during the COVID-19 pandemic in Japan, with no clear evidence of a negative effect on the prescription of ACEIs and ARBs or in-hospital mortality.

Keywords Coronavirus Disease 2019; Heart failure; In-hospital mortality; Angiotensin-converting enzyme inhibitor; Angiotensin II receptor blocker

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Introduction

The Coronavirus Disease 2019 (COVID-19) pandemic has had unprecedented effects on health care systems and patient care delivery worldwide.[1] In addition to the direct involvement of COVID-19 with cardiovascular organs, the pandemic disrupted health care systems for acute and chronic conditions, such as acute myocardial infarction and heart failure (HF), at the patient and health care provider levels.[2–5] Recent studies from the EU[6–9] and the USA[10,11] have revealed a substantial decrease in hospitalization rates for acute myocardial infarction with a sustained decrease in the proportion of urgent percutaneous coronary interventions and increased risk-adjusted mortality rates.

Although decreased hospitalizations for acute coronary syndrome have been reported during the COVID-19 pandemic, the implications for hospitalizations due to the more severe HF are not well understood. The EU,[12,13] the

USA,[14–17] and other regions[18,19] have reported reduced hospitalizations due to HF. There is, however, a paucity of data on the trends and management of HF cases during the pandemic from Japan and East Asia, the region that was affected earlier during the COVID-19 pandemic.

In addition, concerns have been raised regarding a potential increase in susceptibility to COVID-19 from using angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) and subsequent up-regulation of angiotensin-converting enzyme 2.[20–22] On the other hand, the abrupt withdrawal of ACEIs and ARBs from patients with HF may result in decompensated HF and adverse outcomes.[23–25]

Therefore, we sought to define changes in the volume of urgent HF hospitalizations from the COVID-19 state of emergency in Japan via an interrupted time series analysis. We also investigated changes in the prescription of ACEIs and ARBs, and in-hospital mortality during the COVID-19 pandemic.

Methods

Data source and study participants

This retrospective cohort study analysed data extracted from the Diagnosis Procedure Combination (DPC) database collected from April 2018 to September 2020. The DPC/per-diem payment system (PDPS) is a Japanese prospective payment system applied to acute care hospitals. There were 1730 hospitals adopting the DPC/PDPS in 2018, which accounted for 54% (482 618 out of 891 872) of all general beds in Japanese hospitals in 2018. The DPC data consist of claims and discharge summaries, including the International Classification of Diseases, Tenth Revision (ICD-10) codes for classifying the primary diagnosis, the cause of admission, the most and second-most medical-resource-intensive diagnoses, up to 10 comorbidities, and 10 complications. The DPC data also contain codes of all services and medications provided during each hospitalization as well as PDPS information. In the present study, administrative data from 583 hospitals were available during the COVID-19 pandemic period. For evaluation, we included all hospital inpatients that provided DPC data continuously during the study period.

The study period started on 1 April 2018 (1st week) and ended on 4 July 2020 (118th week); all inpatients whose admission date was within this period were included. The ICD-10 classifications were used for defining comorbidities (Supporting Information, *Table S1*). This study included patients aged 18 years or older with a diagnosis of HF. We defined HF cases as ICD-10, I50.x with unscheduled admissions. We determined unscheduled admissions, other than planned or scheduled hospitalizations, using a specific DPC variable. The recalibrated Elixhauser Comorbidity Index was calculated based on a previously described coding algorithm.[26–28] This study was conducted in accordance with the principles of the Declaration of Helsinki, and the study was approved by the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine (approval number: R0135) with a waiver of informed consent prior to data extraction from the database.

The primary outcome measure was the change in the weekly number of HF hospitalizations before and after Japan's COVID-19 state of emergency. Secondary outcome measures included the prescription rates ACEIs and ARBs, and in-hospital mortality among HF patients.

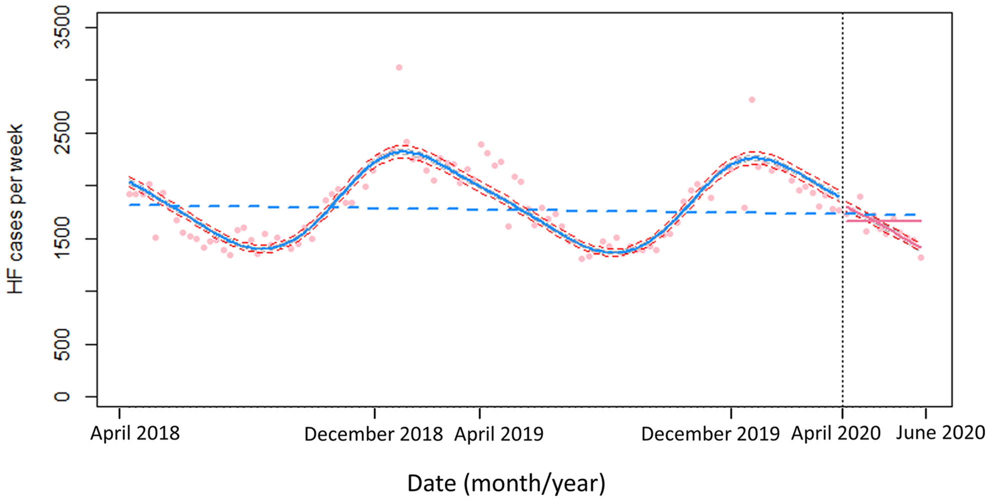
Statistical analysis

Continuous variables were expressed as the median and the interquartile range. Comparisons between the two groups (before and after the state of emergency) for continuous variables were assessed by Mann–Whitney *U* tests. Categorical data were compared using χ^2 or Kruskal–Wallis tests, as appropriate. Statistical significance was set at $P < 0.05$ (two-tailed). Statistical analyses were performed with R Version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria) using R packages 'forecast', 'tsModel', 'tseries', 'foreign', 'lmtest', 'Epi', 'splines', 'vcd', 'ggplot2', 'nlme', 'car', and 'MASS'.

Interrupted time series analyses

Interrupted time series analysis was used to compare HF hospitalizations before and after the COVID-19 state of emergency. Weekly numbers of HF hospitalizations are presented as dots in *Figure 1*. Segmented regression analysis was used to verify changes in the trend and level over time.[29] A 1 week time unit was selected in order to provide optimal precision to the model. Because the Japanese government announced the state of emergency on 7 April 2020, the first week of April 2020 was used as the identified breakpoint. Accordingly, HF cases were divided into one of two periods for analysis, either before (the first week of April 2018 to the first week of April 2020) or after (the second week of April 2020 to the first week of July 2020) the state of emergency was declared. The number of HF admissions in the post-state of emergency period was compared with the expected estimates had the state of emergency not occurred to determine the state of emergency's effect on hospitalizations. Segmented regression analysis was performed to identify the level and trend changes in weekly HF hospitalizations during the pandemic, with consideration given to time dependence in the model. Seasonal variation was taken into account by including harmonic terms (sines and cosines).

Figure 1 Interrupted time series analysis for HF cases per week. The number of HF cases per week is plotted on the *y*-axis and the date (year and month) on the *x*-axis. The red dots show the number of HF cases. The solid lines show the predicted trends based on the seasonally adjusted regression model before (blue) and after (red) April 2020. The grey dashed line shows the 95% confidence interval. The red dashed line shows the 95% prediction interval. The horizontal lines represent the linear predicted values through the study period (dashed, blue) and after the state of emergency was declared (solid, red). The vertical dotted line denotes the declaration of the state of emergency in Japan. HF, heart failure.



The changes in weekly proportions of in-hospital mortality and prescription of ACEIs and/or ARBs over time were also assessed by interrupted time series analysis with identical conditions (time unit, breakpoint, grouping periods, and segmented regression model) as described above. For the evaluation of in-hospital deaths and drug prescriptions, HF cases per week were included as an offset term to adjust for any potential changes in HF inpatient cases over time. The validity of the model was assessed with correlograms (autocorrelation and partial autocorrelation functions) and residual plots.

Secondary and sensitivity analysis

Secondary analysis was performed between 2018 and 2019 by the interrupted time series analysis with a breakpoint of April 2019 to ascertain that April 2020 have a different impact due to the COVID-19 pandemic. Another secondary analysis for the evaluation of HF cases per month, the Japanese population per month was included as an offset term to adjust for any potential changes in the Japanese population over time. Sensitivity analysis was done by changing the break point and evaluating the segmented regression model for each break point. Candidate break points were as follows: (i) 11 March 2020, the World Health Organization has declared the COVID-19 pandemic. (ii) End-March, 2020, in Japan, the number of COVID-19 infections substantially increased in this period. (iii) 7 April 2020, the Japanese government declared the state of emergency.

There are two outlier points in the data. These points in time correspond to the public holiday at the end of the year in Japan. It is known that hospitalization for cardiovascular diseases increases during this period every year. Thus, we conducted a sensitivity analysis controlling for these wild data points. The point can be controlled for in the model by entering an indicator variable that has value 1 in that period and 0 in all others.

Results

Overall study population

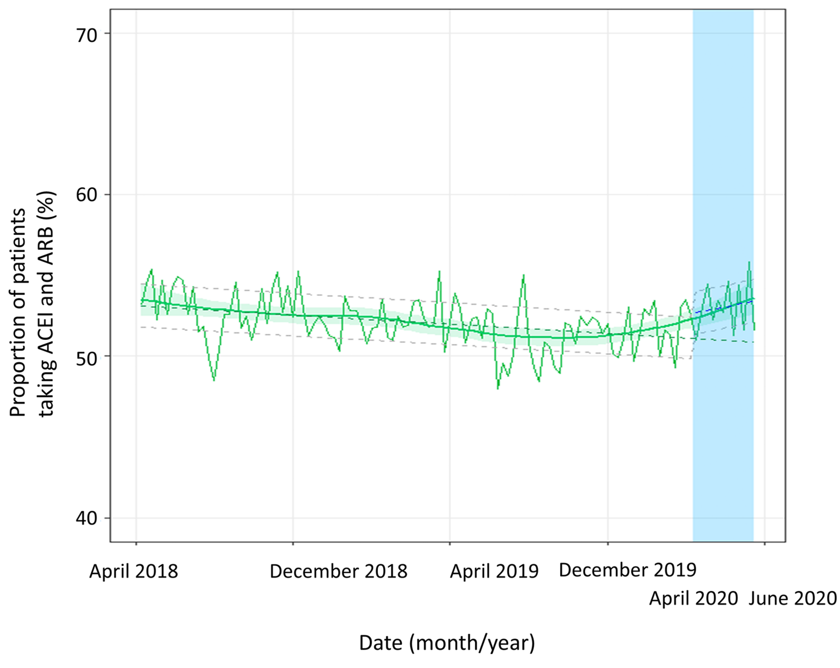
There were 213 784 HF cases requiring hospitalization during the study period [age; 83.0 [75.0, 89.0] years; sex (male); 110 317 cases (51.6%)], among which 90.9% of cases were admitted before Japan's state of emergency was declared, with only 19 363 cases (10.1%) admitted thereafter (*Table 1*). Although patient demographics and drug prescriptions were consistent across the periods, patients with HF hospitalized during the COVID-19 period (after the state of emergency was declared) were more frequently males, had dyslipidaemia as a comorbidity, and were prescribed ACEIs and/or ARBs, beta-blockers, and anti-aldosterone blockers. The duration of hospitalization for HF was similar throughout the entire study period, with a median of 17.0 days. In-hospital mortality was 10.5% (22 547 cases) across the total cohort, with 20 555 deaths (10.6%) before the state of emergency and 1992 deaths (10.3%) thereafter (*Table 1*).

Table 1 Patient characteristics

	All HF (N = 213 784)	Before COVID-19 (n = 194 421)	After COVID-19 (n = 19 363)	P-value
Demographics				
Age, years[a]	83.0 [75.0, 89.0]	83.0 [75.0, 89.0]	83.0 [75.0, 89.0]	0.35
Sex (male), *n* (%)	110 317 (51.6)	100 122 (51.5)	10 195 (52.7)	<0.01
Comorbidities				
Hypertension, *n* (%)	113 363 (53.0)	103 008 (53.0)	10 355 (53.5)	0.19
DM, *n* (%)	63 729 (29.8)	58 009 (29.8)	5720 (29.5)	0.40
Dyslipidaemia, *n* (%)	49 289 (23.1)	44 666 (23.0)	4623 (23.9)	<0.01
Smoking history, *n* (%)	45 207 (41.3)	30 319 (41.3)	14 888 (41.2)	0.71
Prior MI, *n* (%)	17 119 (8.0)	15 624 (8.0)	1495 (7.7)	0.13
Stroke, *n* (%)	3797 (1.8)	3466 (1.8)	331 (1.7)	0.48
PAD, *n* (%)	501 (0.2)	450 (0.2)	51 (0.3)	0.39
Previous heart failure, *n* (%)	19 212 (9.0)	17 443 (9.0)	1769 (9.1)	0.45
Elixhauser Comorbidity Index	5 [0, 7]	5 [0, 7]	5 [0, 7]	0.25
Medications				
ACEI/ARB, *n* (%)	111 563 (52.2)	101 293 (52.1)	10 270 (53.0)	0.01
Beta-blocker, *n* (%)	132 658 (62.1)	120 225 (61.8)	12 433 (64.2)	<0.01
Aldosterone receptor antagonist, *n* (%)	98 404 (46.0)	89 167 (45.9)	9237 (47.7)	<0.01
Duration of hospitalization, days	17.0 [11.0, 28.0]	17.0 [11.0, 28.0]	17.0 [11.0, 27.0]	<0.01
In-hospital mortality, *n* (%)	22 547 (10.5)	20 555 (10.6)	1992 (10.3)	0.23

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; COVID-19, Coronavirus Disease 2019; DM, diabetes mellitus; HF, heart failure; MI, myocardial infarction; PAD, peripheral arterial disease.
[a]Indicates values that are medians [first quartile, third quartile].

Figure 2 Interrupted time series analysis for ACEI and ARB prescriptions per month. The proportion of ACEI and ARB prescriptions per week is plotted on the *y*-axis and the date (year and month) is on the *x*-axis. The curved green line represents a locally estimated smoothing spline fitted through the weekly proportions. The shaded green area shows the 95% confidence interval. The grey dashed line shows the 95% prediction interval. The horizontal green dashed line shows the linear predicted values through the entire study period, while the horizontal blue dashed line shows the linear predicted values after April 2020. The blue shaded area shows the period after the declaration of the state of emergency in Japan. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.



Interrupted time series analyses for changes in heart failure admissions

Figure 1 demonstrates the weekly numbers of HF cases with the interrupted time series analysis. The COVID-19 pandemic led to a significant and immediate decrease in HF admissions per week [−3.6%, 95% confidence interval (CI): −0.3% to −6.7%, P = 0.03], which corresponded with the absolute reduction of 77.5 HF cases per week between the two periods. Thereafter, HF hospitalizations remained at a lower level

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without a significant change in the trend of HF admissions per week during the pandemic (slope change: −0.04%; 95% CI: −0.4% to 0.5%, *P* = 0.86). The trend in HF hospitalizations from January through June 2020 and the corresponding period in 2019 are displayed in Supporting Information, *Figure S1*. After the state of emergency was declared, the number of HF admissions continued to decline between April and June 2020.

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers prescriptions during COVID-19 pandemic

Prescriptions of ACEIs and ARBs for HF inpatients before and after Japan's state of emergency are shown in *Figure 2*. The proportions of ACEIs and ARBs prescriptions were not significantly different between the study periods (change: 4.2%; 95% CI: −0.3% to 8.9%, *P* = 0.07), although there was a decrease in the absolute number of patients with worsening HF. There were no significant changes in prescription trends for ACEIs and ARBs with interrupted time series analysis (slope change: −0.1%; 95% CI: −0.2% to 0.1%, *P* = 0.38).

In-hospital mortality

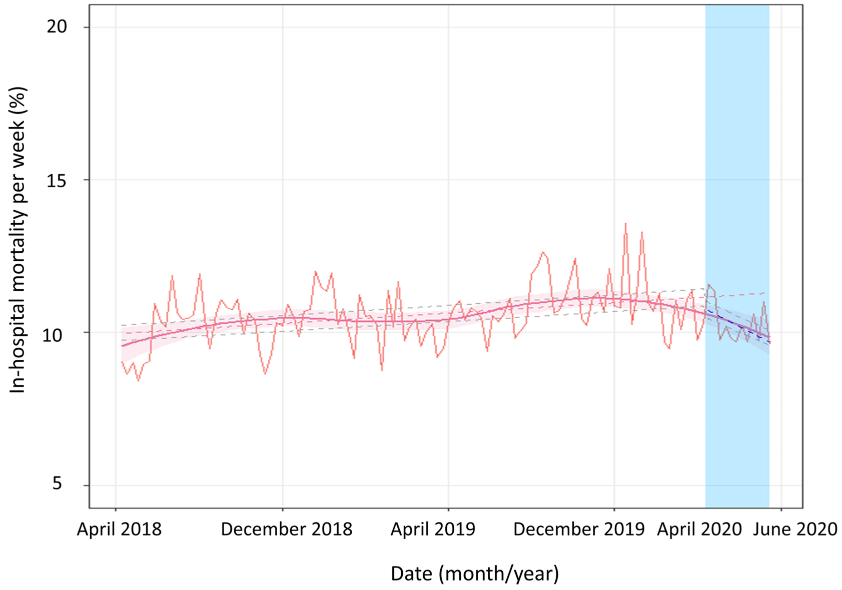
Among HF inpatients, interrupted time series analysis revealed that there was no significant change in the proportion of in-hospital deaths associated with the COVID-19 pandemic (change: 5.3%; 95% CI: −4.9% to 16.6%, *P* = 0.32; slope change: −1.7%; 95% CI: −3.1% to −0.4%, *P* = 0.01; *Figure 3*).

Secondary and sensitivity analysis

To determine whether our findings were specific to COVID-19 pandemic, we conducted post hoc, additional secondary and sensitivity analyses. A secondary analysis showed that HF admission cases with the breakpoint of April 2019 did not significantly decrease as seen with the breakpoint of April 2020 during COVID-19 pandemic but rather increased (change: 5.4%; 95% CI: 3.4% to 7.6%, $P < 0.001$).

We refit the model substituting the breakpoint to candidate breakpoints; (i) 11 March 2020, the World Health Organization has declared the COVID-19 pandemic. (ii) End-March, 2020, in Japan, the number of COVID-19 infections substantially increased in this period. The COVID-19 pandemic was accompanied by significant and immediate decreases in HF admissions cases for both breakpoints (change: −3.6%, 95% CI: −0.3% to −6.7%, *P* = 0.03 and change: −3.6%, 95% CI: −0.3% to −6.7%, *P* = 0.03, respectively). Another secondary analysis for the evaluation of HF cases per month, the number of HF admission led to a significant and immediate decrease in HF admissions per month (−33.3%, 95% CI: −35.9% to −30.6%, $P < 0.001$) between the study periods.

Figure 3 Interrupted time series analysis for in-hospital deaths per week. The proportion of in-hospital deaths per week is plotted on the *y*-axis and the date (year and month) is on the *x*-axis. The red curved line shows a locally estimated smoothing spline fitted through the weekly proportions. The shaded red area shows the 95% confidence interval. The grey dashed line shows the 95% prediction interval. The horizontal red dashed line represents the linear predicted values, and the horizontal blue dashed line represents the linear predicted values after April 2020. The blue shaded area shows the time period after the declaration of the state of emergency in Japan.



We added the indicator variable for wild data points to test the robustness of our findings based on the model controlling for wild data points. Sensitivity analysis verified that our findings were qualitatively unaffected by controlling for these wild data points (change: −4.9%, 95% CI: −8.0% to −1.7%, $P = 0.003$).

Discussion

The main findings of our study suggest that (i) urgent hospitalizations due to HF significantly decreased immediately after the state of emergency was declared in Japan; (ii) prescriptions for ACEIs and ARBs were similar before and after the state of emergency; and (iii) there was no significant deterioration of in-hospital mortality before and after the declaration of the state of emergency in Japan.

Firstly, unprecedented reductions in HF hospitalizations were documented in our Japanese cohort following the state of emergency. A range of plausible explanations can be proposed for this observation.[12–16,18,19,30] The declaration of the state of emergency and fear of being infected with COVID-19 in the hospital setting may have kept HF patients away from hospitals. Also, society-wide measures introduced to reduce transmission, such as social distancing, hand hygiene, and wearing masks, may have effectively reduced the incidence of other common respiratory viral infections. Respiratory infections are an acute precipitant exacerbating HF.[31] As such, reducing respiratory infections may consequently limit HF hospitalizations. In Japan, there was a marked reduction in the number of inpatients with non-COVID-19 acute respiratory infections during the COVID-19 pandemic.[32,33] Therefore, this factor could be a contributor to reducing infection-related hospital admissions of HF patients. Furthermore, because medical resources were transferred to prioritize COVID-19 patients, there may have been delays in the treatment of less urgent HF patients. Of these plausible explanations, the most worrisome is that HF patients may have been reluctant to seek urgent care for fear of contracting COVID-19.[2,4,34]

Secondly, concern exists regarding the interaction between severe acute respiratory syndrome coronavirus-2 and angiotensin-converting enzyme 2 potentially increasing susceptibility to COVID-19. This concern led to a behavioural change in which both health care providers and patients suspended the prescription and use of ACEIs or ARBs in the previous studies.[20–22] However, the proportion of ACEIs and ARBs prescriptions did not differ before or after the pandemic in the present study. Similarly, recent investigations support the maintenance of ACEIs or ARBs prescriptions during the COVID-19 pandemic.[23–25] In this study, there was no significant increase in susceptibility to COVID-19 among HF patients receiving ACEIs or ARBs, and as such, there was no clear evidence for ceasing ACEIs and ARBs prescriptions prophylactically. Thus, the maintenance of ACEIs or ARBs prescriptions may have contributed to avoiding a rise in mortality rates.

Thirdly, in-hospital mortality due to HF did not worsen during the COVID-19 pandemic. Previous studies have shown that in-hospital mortality was worse among patients admitted during the COVID-19 pandemic, and there were higher rates of class III or IV symptoms (New York Heart Association) when compared with the same period in 2019.[18,19] Our results, which contradict these previous studies, may reflect the extent to which the pandemic affected the health care system overall. For example, disruptions in the health care system in northern Italy in the early stages of the pandemic[6,35] resulted in a limited supply of medical resources. Consequently, the demands for care exceeded the available resources, which limited the quality of medical care for other diseases. In Japan, we presume that resources and health care providers in cardiovascular care units were adequately resourced and still able to ensure appropriate acute care for all HF patients requiring urgent attention.[36]

This study had several limitations. Firstly, only hospitalized HF patients were included, which does not provide information regarding HF cases in the outpatient setting. Survival bias should also be considered in patients hospitalized with HF. Our study also lacked information about several factors associated with in-hospital mortality, such as ejection fraction, renal function, and natriuretic peptide levels. Segmented regression analysis of interrupted time series data allows us to assess how much a well-defined intervention changed an outcome of interest. Interrupted time series (ITS) design is also increasingly being used to evaluate the impact of interventions ranging from national public health policy implementation to health impact of natural disaster, political, and sociocultural events. In case of natural disaster, like COVID-19 pandemic, it may be difficult to define when the intervention began. A sufficient number of time points before and after the intervention are needed to conduct segmented regression analysis. We had deal with relatively short time series data with 30 monthly measures. Thus, further time series analyses are warranted to verify current findings controlling for temporal and seasonal trends with use of long-term longitudinal data.

In conclusion, we demonstrated a decline in HF cases in acute cardiovascular care settings during the COVID-19 pandemic. Furthermore, there was no clear evidence of a negative effect of the pandemic on the prescription of ACEIs and ARBs, nor in-hospital mortality.

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Conflict of interest

None declared.

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Supporting information

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

Figure S1. Heart failure hospitalizations trends from January through June, 2020 and the corresponding period in 2019. The number of HF cases per month is plotted on the y-axis, and the month is on the x-axis. HF, heart failure.

Table S1. Conditions and Corresponding ICD-10 Codes.

Table S2. The monthly volume of heart failure admissions from April 2018 to June 2020.

References

1. Banerjee A, Pasea L, Harris S, Gonzalez-Izquierdo A, Torralbo A, Shallcross L, Noursadeghi M, Pillay D, Sebire N, Holmes C, Pagel C, Wong WK, Langenberg C, Williams B, Denaxas S, Hemingway H. Estimating excess 1-year mortality associated with the COVID-19 pandemic according to underlying conditions and age: a population-based cohort study. *Lancet* 2020; **395**: 1715–1725.
2. Bhatt AS, Moscone A, McElrath EE, Varshney AS, Claggett BL, Bhatt DL, Januzzi JL, Butler J, Adler DS, Solomon SD, Vaduganathan M. Fewer hospitalizations for acute cardiovascular conditions during the COVID-19 pandemic. *J Am Coll Cardiol* 2020; **76**: 280–288.
3. Ebinger JE, Shah PK. Declining admissions for acute cardiovascular illness: the COVID-19 paradox. *J Am Coll Cardiol* 2020; **76**: 289–291.
4. Toniolo M, Negri F, Antonutti M, Masè M, Facchin D. Unpredictable fall of severe emergent cardiovascular diseases hospital admissions during the COVID-19 pandemic: experience of a single large center in Northern Italy. *J Am Heart Assoc* 2020; **9**: e017122.
5. Piccolo R, Bruzzese D, Mauro C, Aloia A, Baldi C, Boccalatte M, Bottiglieri G, Briguori C, Caiazzo G, Calabrò P, Cappelli-Bigazzi M, de Simone C, di Lorenzo E, Golino P, Monda V, Perrotta R, Quaranta G, Russolillo E, Scherillo M, Tesorio T, Tuccillo B, Valva G, Villari B, Tarantini G, Varricchio A, Esposito G, Avvedimento M, Bianchi RM, Capobianco S, Carpinella G, Crisci M, Esposito L, Fattore L, Fimiani L, Formigli D, Golino M, Laurenzano E, Leone A, Magliulo F, Niglio T, Padalino R, Pastore F, Serino F, Scotto di Uccio F, Visconti G. Population trends in rates of percutaneous coronary revascularization for acute coronary syndromes associated with the COVID-19 outbreak. *Circulation* 2020; **141**: 2035–2037.
6. De Filippo O, D'Ascenzo F, Angelini F, Bocchino PP, Conrotto F, Saglietto A, Secco GG, Campo G, Gallone G, Verardi R, Gaido L. Reduced rate of hospital admissions for ACS during Covid-19 outbreak in Northern Italy. *N Engl J Med* 2020; **383**: 88–89.
7. Mafham MM, Spata E, Goldacre R, Gair D, Curnow P, Bray M, Hollings S, Roebuck C, Gale CP, Mamas MA, Deanfield JE, de Belder MA, Luescher TF, Denwood T, Landray MJ, Emberson JR, Collins R, Morris EJA, Casadei B, Baigent C. COVID-19 pandemic and admission rates for and management of acute coronary syndromes in England. *Lancet* 2020; **396**: 381–389.
8. Metzler B, Siostrzonek P, Binder RK, Bauer A, Reinstadler SJ. Decline of acute coronary syndrome admissions in Austria since the outbreak of COVID-19: the pandemic response causes cardiac collateral damage. *Eur Heart J* 2020; **41**: 1852–1853.
9. Scholz KH, Lengenfelder B, Thilo C, Jeron A, Stefanow S, Janssens U, Bauersachs J, Schulze PC, Winter KD, Schröder J, vom Dahl J, von Beckerath N, Seidl K, Friede T, Meyer T. Impact of COVID-19 outbreak on regional STEMI care in Germany. *Clin Res Cardiol* 2020; **109**: 1511–1521.
10. Gluckman TJ, Wilson MA, Chiu ST, Penny BW, Chepuri VB, Waggoner JW, Spinelli KJ. Case rates, treatment approaches, and outcomes in acute myocardial infarction during the coronavirus disease 2019 pandemic. *JAMA Cardiol* 2020; **5**: 1419–1424.
11. Garcia S, Albaghdadi MS, Meraj PM, Schmidt C, Garberich R, Jaffer FA, Dixon S, Rade JJ, Tannenbaum M, Chambers J, Huang PP, Henry TD. Reduction in ST-segment elevation cardiac catheterization laboratory activations in the United States during COVID-19 pandemic. *J Am Coll Cardiol* 2020; **75**: 2871–2872.
12. Bromage DI, Cannatà A, Rind IA, Gregorio C, Piper S, Shah AM, McDonagh TA. The impact of COVID-19 on heart failure hospitalization and management: report from a heart failure unit in London during the peak of the pandemic. *Eur J Heart Fail* 2020; **22**: 978–984.
13. Konig S, Hohenstein S, Meier-Hellmann A, Kuhlen R, Hindricks G, Bollmann A, Helios Hospitals, Germany. In-hospital care in acute heart failure during the COVID-19 pandemic: insights from the German-wide Helios hospital network. *Eur J Heart Fail* 2020; **22**: 2190–2201.
14. Hall ME, Vaduganathan M, Khan MS, Papadimitriou L, Long RC, Hernandez GA, Moore CK, Lennep BW, Mcmullan MR, Butler J. Reductions in heart failure hospitalizations during the COVID-19 pandemic. *J Card Fail* 2020; **26**: 462–463.
15. Barghash MH, Pinney SP. Heart failure in the COVID-19 pandemic: where has all New York's congestion gone? *J Card Fail* 2020; **26**: 477–478.
16. McIlvennan CK, Allen LA, Devore AD, Granger CB, Kaltenbach LA, Granger BB. Changes in care delivery for patients with heart failure during the COVID-19 pandemic: results of a multicenter survey. *J Card Fail* 2020; **26**: 635–636.
17. Cox ZL, Lai P, Lindenfeld J. Decreases in acute heart failure hospitalizations dur-

ing COVID-19. *Eur J Heart Fail* 2020; **22**: 1045–1046.
18. Frankfurter C, Buchan TA, Kobulnik J, Lee DS, Luk A, McDonald M, Ross HJ, Alba AC. Reduced rate of hospital presentations for heart failure during the COVID-19 pandemic in Toronto, Canada. *Can J Cardiol* 2020; **36**: 1680–1684.
19. Toner L, Koshy AN, Ko J, Driscoll A, Farouque O. Clinical characteristics and trends in heart failure hospitalizations: an Australian experience during the COVID-19 lockdown. *JACC Heart Fail* 2020; **8**: 872–875.
20. Tomasoni D, Italia L, Adamo M, Inciardi RM, Lombardi CM, Solomon SD, Metra M. COVID-19 and heart failure: from infection to inflammation and angiotensin II stimulation. Searching for evidence from a new disease. *Eur J Heart Fail* 2020; **22**: 957–966.
21. Patel AB, Verma A. COVID-19 and angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: what is the evidence? *JAMA* 2020; **323**: 1769–1770.
22. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin-angiotensin-aldosterone system inhibitors in patients with Covid-19. *N Engl J Med* 2020; **382**: 1653–1659.
23. Bean DM, Kraljevic Z, Searle T, Bendayan R, Kevin O, Pickles A, Folarin A, Roguski L, Noor K, Shek A, Zakeri R. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers are not associated with severe COVID-19 infection in a multi-site UK acute hospital trust. *Eur J Heart Fail* 2020; **22**: 967–974.
24. Rico-Mesa JS, White A, Anderson AS. Outcomes in patients with COVID-19 infection taking ACEI/ARB. *Curr Cardiol Rep* 2020; **22**: 31.
25. Amat-Santos IJ, Santos-Martinez S, Lopez-Otero D, Nombela-Franco L, Gutierrez-Ibanes E, Del Valle R, Muñoz-García E, Jiménez-Diaz VA, Regueiro A, González-Ferreiro R, Benito T. Ramipril in high-risk patients with COVID-19. *J Am Coll Cardiol* 2020; **76**: 268–276.
26. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, Saunders LD, Beck CA, Feasby TE, Ghali WA. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care* 2005; **43**: 1130–1139.
27. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. *Med Care* 1998; **36**: 8–27.
28. Shin JH, Kunisawa S, Imanaka Y. New outcome-specific comorbidity scores excelled in predicting in-hospital mortality and healthcare charges in administrative databases. *J Clin Epidemiol* 2020; **126**: 141–153.
29. Bernal JL, Cummins S, Gasparrini A. Interrupted time series regression for the evaluation of public health interventions: a tutorial. *Int J Epidemiol* 2017; **46**: 348–355.
30. Bromage DI, Cannata A, Rind IA, Gregorio C, Piper S, Shah AM, McDonagh TA. The impact of COVID-19 on heart failure hospitalization and management: report from a heart failure unit in London during the peak of the pandemic. *Eur J Heart Fail* 2020; **22**: 978–984.
31. Tsuyuki RT, McKelvie RS, Arnold JM, Avezum A Jr, Barretto AC, Carvalho AC, Isaac DL, Kitching AD, Piegas LS, Teo KK, Yusuf S. Acute precipitants of congestive heart failure exacerbations. *Arch Intern Med* 2001; **161**: 2337–2342.
32. Nagano H, Takada D, Shin JH, Morishita T, Kunisawa S, Imanaka Y. Hospitalization of mild cases of community-acquired pneumonia decreased more than severe ones during the COVID-19 epidemic. *Int J Infect Dis* 2021; **106**: 323–328.
33. Kishimoto K, Bun S, Shin JH, Takada D, Morishita T, Kunisawa S, Imanaka Y. Early impact of school closure and social distancing for COVID-19 on the number of inpatients with childhood non-COVID-19 acute infections in Japan. *Eur J Pediatr* 2021; **180**: 2871–2878.
34. Reza N, DeFilippis EM, Jessup M. Secondary impact of the COVID-19 pandemic on patients with heart failure. *Circ Heart Fail* 2020; **13**: e007219.
35. Roffi M, Guagliumi G, Ibanez B. The obstacle course of reperfusion for ST-segment-elevation myocardial infarction in the COVID-19 pandemic. *Circulation* 2020; **141**: 1951–1953.
36. Ishii H, Amano T, Yamaji K, Kohsaka S, Yokoi H, Ikari Y. Implementation of percutaneous coronary intervention during the COVID-19 pandemic in Japan—nationwide survey report of the Japanese Association of Cardiovascular Intervention and Therapeutics for Cardiovascular Disease. *Circ J* 2020; **84**: 2185–2189.

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