ESC European Society of Cardiology

European Heart Journal Open (2022) **2**, 1–10
https://doi.org/10.1093/ehjopen/oeac051

ORIGINAL ARTICLE
Epidemiology & prevention

Prevalence and prognostic implications of myocardial injury in patients with influenza

Anna M Nordenskjöld [1,*], Niklas Johansson[2], Erik Sunnefeldt[1], Simon Athlin[2], and Ole Fröbert[1,3,4,5]

[1]Department of Cardiology, Faculty of Medicine and Health, Örebro University, 70281 Örebro, Sweden; [2]Department of Infectious Diseases, Faculty of Medicine and Health, Örebro University, 70281 Örebro, Sweden; [3]Steno Diabetes Center Aarhus, Aarhus University Hospital, 8200 Aarhus N, Denmark; [4]Department of Clinical Medicine, Faculty of Health, Aarhus University, 8000 Aarhus, Denmark; and [5]Department of Clinical Pharmacology, Aarhus University Hospital, 8200 Aarhus N, Denmark

Received 12 April 2022; revised 1 June 2022; accepted 14 June 2022; online publish-ahead-of-print 8 August 2022

Handling Editor: Jonas Faxén

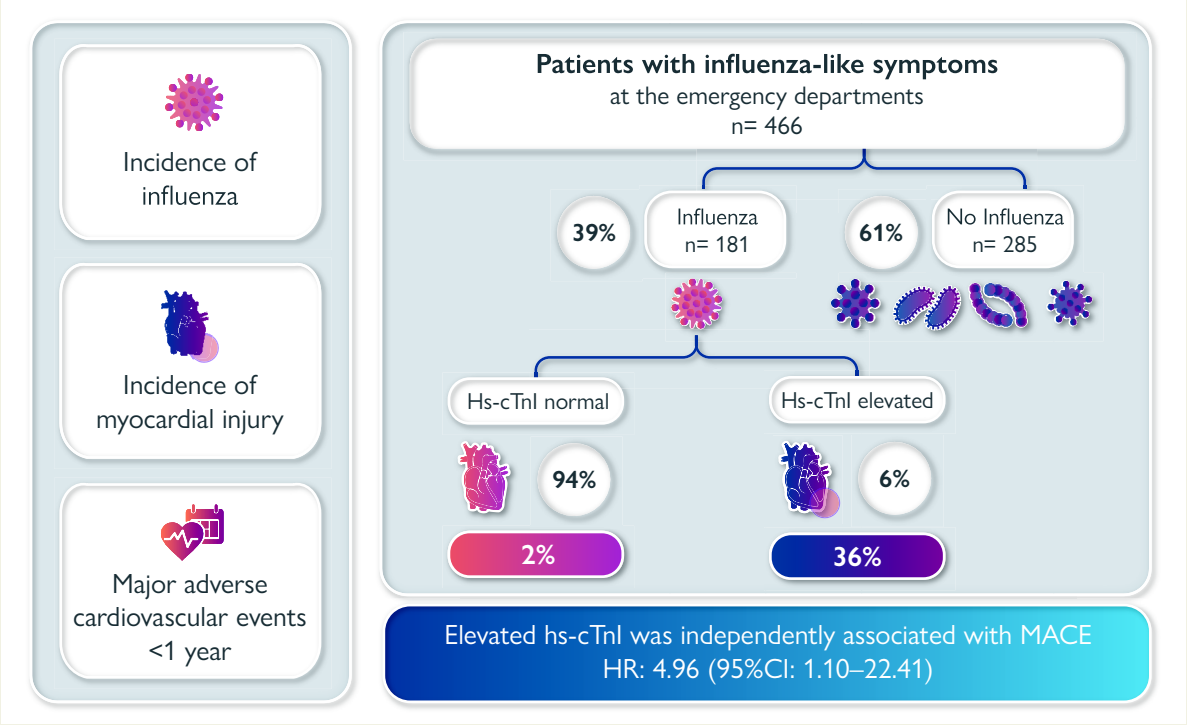
Aims Influenza may cause myocardial injury and trigger acute cardiovascular events. The aim of this study was to investigate the prevalence and prognostic implications of elevated high-sensitivity cardiac troponin I (hs-cTnI) in patients with influenza.

Methods and results In this prospective cohort study, we consecutively enrolled patients with influenza-like illness from two emergency departments in Sweden during three seasons of influenza, 2017–20. Ongoing Influenza infection was diagnosed by polymerase chain reaction and blood samples were collected for later analysis of hs-cTnI. All patients were followed-up for a composite endpoint of major adverse cardiovascular events (MACE) including death, myocardial infarction, unstable angina, heart failure, atrial fibrillation, and stroke within 1 year. Of the 466 patients with influenza-like symptoms, 181 (39%) were positive for influenza. Fifty (28%) patients were hospitalized. High-sensitivity cTnI was elevated in 11 (6%) patients and 8 (4%) experienced MACE. In univariate analyses, MACE was associated with age [hazard ratio (HR): 1.14, 95% confidence interval (CI): 1.05–1.23], hypertension (HR 5.56, 95%CI: 1.12–27.53), estimated glomerular filtration rate (HR: 0.94, 95%CI: 0.91–0.97), and elevated hs-cTnI (HR: 18.29, 95%CI: 4.57–73.24), N-terminal prohormone of brain natriuretic peptide (HR: 14.21, 95%CI: 1.75–115.5), hs-CRP (HR: 1.01, 95%CI: 1.00–1.02), and white blood cell count (HR: 1.12, 95%CI: 1.01–1.25). In multivariate analysis, elevated hs-cTnI was independently associated with MACE (HR: 4.96, 95%CI: 1.10–22.41).

Conclusion The prevalence of elevated hs-cTnI is low in unselected patients with influenza. Elevated hs-cTnI was associated with poor prognosis. A limitation is that the estimated associations are uncertain due to few events.

* Corresponding author. Tel: +46 19 602 54 05, Fax: +46 19 602 54 38, Email: anna.nordenskjold@regionorebrolan.se

Graphical Abstract



Keywords Influenza • Cardiac troponin • Prognosis

Background

Annual epidemics of influenza are estimated to result in 3–5 million cases of serious disease and 290 000–650 000 respiratory deaths worldwide.[1] Although influenza is characterized predominately by respiratory manifestations, myocarditis,[2–4] and exacerbation of underlying chronic cardiac diseases, such as congestive heart failure and atrial fibrillation, are not uncommon.[4–7] In addition, evidence has suggested that influenza may be a cause of acute myocardial injury and a trigger off acute cardiovascular events.[4,8–15]

Retrospective studies, both case–control and self-controlled case-series, have demonstrated that patients who test positive for influenza are at increased risks of acute myocardial infarction (MI) and stroke.[9,10,14,15] Moreover, concomitant influenza was found to negatively affect the short-term prognosis of patients with MI.[16,17] Protection from influenza has been reported to improve prognosis in patients with MI, and a recent placebo-controlled trial showed that influenza vaccination following MI reduces future cardiovascular events.[18]

Myocardial injury is defined as the detection of an elevated cardiac troponin (cTn) above the 99th percentile upper reference limit and the injury is considered acute if there is a rise and/or fall of cTn values.[19] High-sensitivity immunoassays to measure the concentrations of cTn (hs-cTn) are recommended to detect myocardial injury, regardless of whether the underlying mechanism is ischaemic or non-ischaemic.[19]

To date, only a few studies have measured hs-cTn in patients with influenza, with these studies showing that the prevalence of troponin positivity ranges widely and is dependent on the cohort studied.[20–24] However, three recent studies have reported that increased hs-cTn concentrations were associated with acute cardiac events and death within 30 days.[23–25]

Prospective studies assessing the prevalence of elevated hs-cTn in unselected cohorts and the association of elevated hs-cTn with major adverse cardiovascular events (MACE) are scarce. Therefore, the present study was designed to evaluate the prevalence of elevated high-sensitivity cTnI (hs-cTnI) and other cardiac and inflammatory markers in patients with laboratory-confirmed influenza, and to investigate the prognostic implication of elevated hs-cTnI on MACE in these patients.

Methods

Study design and participants

This prospective cohort study conducted in Region Örebro County, Sweden, included patients aged ≥18 years who presented with influenza-like symptoms to the emergency departments (EDs) of Örebro

University Hospital and Karlskoga County Hospital during the 2017/2018, 2018/2019, and 2019/2020 influenza seasons. The annual influenza season is defined as occurring between October 1 and April 30.[26] Recruitment of patients during the 2019/2020 influenza season was terminated on 17 February 2020, due to the developing Coronavirus disease 2019 (COVID-19) pandemic.

All patients presenting with influenza-like illness at the EDs and who, due to a strong clinical suspicion of ongoing influenza illness were tested using reverse transcription polymerase chain reaction (RT-PCR) assays, were considered for inclusion. Written informed consent was required for inclusion. The exclusion criteria included an inability to provide informed consent, age <18 years and ongoing symptoms or findings indicating an acute coronary syndrome, pulmonary oedema, haemodynamically significant arrhythmia, or acute stroke.

Data on medical history, vaccination status, duration of illness, and clinical symptoms were collected from participants using questionnaires. An electrocardiogram (ECG) was recorded, and a nasopharyngeal swab was collected for RT-PCR analyses of influenza A and influenza B (Simplexa Flu A/B & RSV, Focus Diagnostics, Cypress, CA, USA). Blood samples were obtained directly after inclusion, at the ED, for subsequent analysis of hs-cTnI and other biomarkers. Plasma was collected in EDTA-containing tubes and stored at −70°C until analysis. Medical charts were consulted 1 year after inclusion to determine the incidence of MACE, defined as a composite of all-cause death, MI, hospitalization due to heart failure, unstable angina, atrial fibrillation, and stroke. The prevalence of myocarditis, other arrhythmias, and Takotsubo syndrome was also recorded.

Previous and later measurements of hs-cTnI vales were also noted during the review of medical charts.

Patients with RT-PCR confirmed influenza were defined as the cases and patients who tested negative for influenza served as controls (*Figure 1*).

The study was performed in accordance with the Declaration of Helsinki and was approved by the Regional Ethical Review Board of Uppsala (2017/220). This trial is registered at www.clinicaltrials.gov: as NCT03339180.

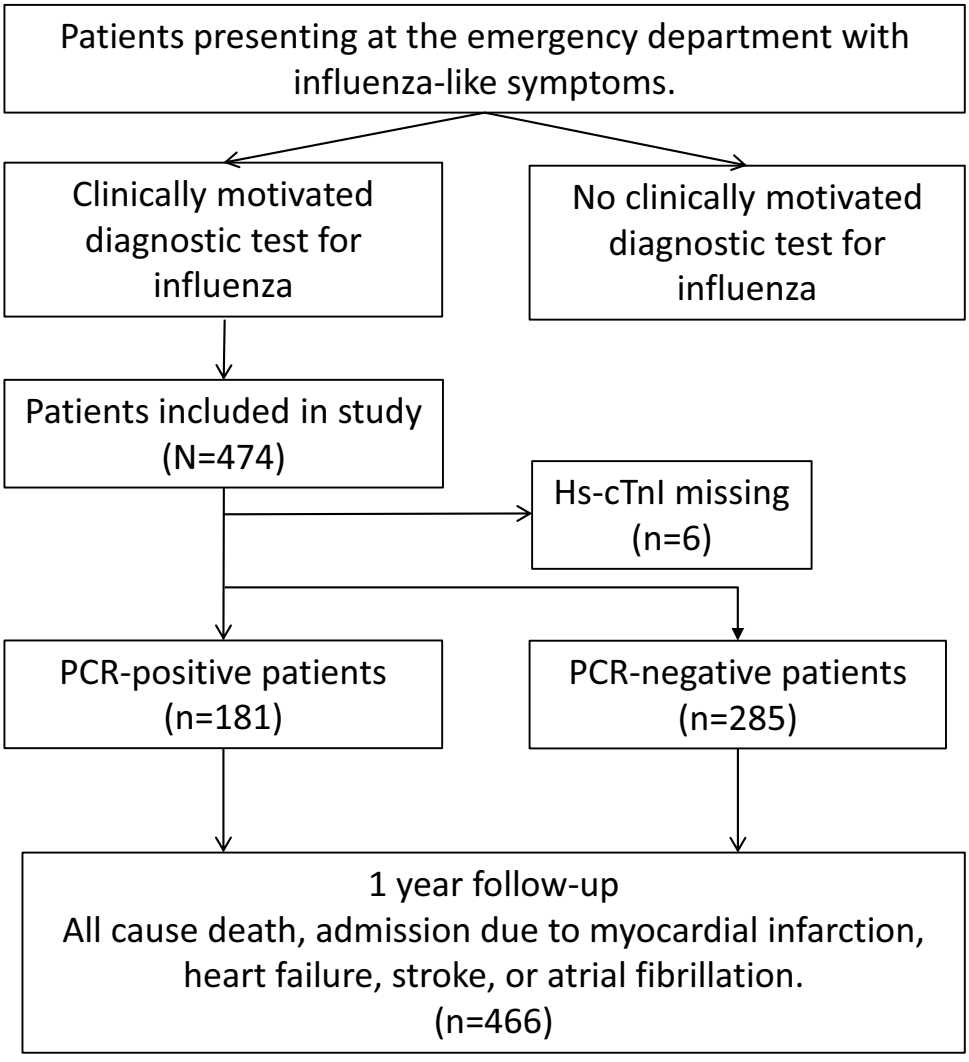


Figure 1 Study cohort. A total of 466 individuals were included, 181 with confirmed influenza, and 285 without confirmed influenza.

Cardiac biomarkers

High-sensitivity cTnI was measured using the hs-cTnI-Centaur assay (ADVIA Centaur TNIH, Siemens Healthcare), which has been reported by the manufacturer of having a population 99th percentile concentration (both sexes) of 47 ng/L with a corresponding coefficient of variation <5%. The sex-adjusted 99th percentiles for men and women are 57 and 37 ng/L, respectively.

N-terminal prohormone of brain natriuretic peptide (NT-proBNP) was measured using the NT-proBNP-Cenatur assay (ADVIA Centaur PBNP-analysis, Siemens Healthcare), with cutoffs of 125 and 450 pg/mL for individuals aged <75 years old and >75 years, respectively, as determined by the manufacturer.

Outcome definitions

Baseline information was obtained from patients at inclusion and from medical charts.

Myocardial injury was defined as the detection of a value of hs-cTn above the 99th percentile upper reference limit.[19] If the review of medical charts revealed earlier or later clinically motivated single or repeated measurements of hs-cTnI, these values were compared with the hs-cTnI value measured at inclusion and the injury was considered acute if there was a rise and/or fall of cTnI values.[27]

Causes of death 1-year after patient inclusion were determined based on International Statistical Classification of Diseases and Related Health Problems, (ICD-10 codes) recorded in medical charts or death certificates. Myocardial infarction was defined as ICD codes I21 and I22, unstable angina as ICD code I20, heart failure as ICD code I50, myocarditis as ICD codes I40 and I41, stroke as ICD code I63, and atrial fibrillation as ICD code I48. Event adjudication was not performed.

Primary and secondary endpoints and endpoint definitions

The primary endpoint was defined as the prevalence of increased hs-cTnI concentrations at the time of inclusion. High-sensitivity cTnI values above the sex-specific 99th percentiles were considered elevated. The secondary endpoint was defined as the time to a composite endpoint of MACE, including all-cause death, admission for MI, unstable angina, heart failure, atrial fibrillation, and stroke.

Statistical analyses

Normally distributed continuous variables are presented as mean ± standard deviation (SD), and non-normally distributed continuous variables as median and inter-quartile range (IQR). Differences between cases controls were assessed by unpaired *t*-tests on original scale or log scale as appropriate. Ordinal variables were assessed with χ^2 tests for trend or Mann–Whitney *U* tests, and differences between proportions were evaluated by Pearson's χ^2 test or Fisher's exact test, as appropriate. Two-sided *P*-values <0.05 were considered statistically significant, with all estimates presented with their 95% confidence intervals (CIs). A small number of missing data did affect some of the other variables and numbers are reported in *Table 1*. For individuals in the influenza group with missing data in categorical variables these were imputed into the largest category and missing data in continuous variables were imputed as the mean or median value as appropriate. *Tables 2 and 3* include imputed data.

Clinical characteristics associated with MACE were evaluated by univariate and multivariate Cox regression analyses. All factors associated with MACE on univariate analyses with a $P < 0.05$ were included in the multivariate model; these included age, hypertension, elevated hs-cTnI, elevated NT-proBNP, estimated glomerular filtration rate, hs-CRP concentration, and white blood cell (WBC) count. In multivariable analysis, hs-cTnI was used as a dichotomous variable, with a cutoff at the 99th percentile, to adjust for sex differences. Due to the low number of events (<10) and comparatively large number of exposures stepwise procedures with both forward and backward analyses were used to ascertain the results further. Hazard ratios (HRs) and their corresponding 95%CI are reported. The association between elevated hs-cTnI and MACE was also evaluated by log-rank test.

High-sensitivity cardiac troponin I was regarded as both a continuous and a categorical variable, with concentrations ≥57 ng/L for men and ≥37 ng/L for women considered elevated. NT-proBNP was also regarded as both a continuous and a categorical variable, with concentrations ≥300 pg/mL considered elevated in the acute setting.[27]

All statistical tests were two-tailed and $P < 0.05$ was regarded as statistically significant. All statistical analyses were performed using the Predictive Analytical SoftWare (PASW statistics 17.03) programme (SPSS Inc, Chicago, IL, USA).

Results

Of the 466 patients who presented to the EDs during three influenza seasons, 181 (39%) tested positive for influenza, including 94 (52%) who were positive for influenza A and 87 (48%) who were positive for influenza B. Both patients with and without influenza had influenza-like symptoms for a median 4 days before inclusion. There was no difference in gender between groups. Patients with influenza were significantly younger, had a higher maximum body temperature, and had a lower rate of previous heart failure than patients without influenza (*Table 1*). In addition, estimated glomerular filtration rate was higher, concentrations of hs-cTnI, NT-proBNP, and hs-CRP were lower; WBC, neutrophil, lymphocyte, and platelets counts were lower; and erythrocyte sedimentation rate was lower in patients with than without influenza (*Table 1*).

Prevalence of elevated high-sensitivity cardiac troponin I

Of the 466 patients in the entire cohort, 43 (9%) had hs-cTnI concentrations above the sex-specific cutoff levels, including 11 (6%) of the 181 influenza positive and 32 (11%) of the 285 influenza negative patients.

Patients with confirmed influenza

Patients with influenza and elevated hs-cTnI were older, had higher NT-proBNP and hs-CRP concentrations, and more often had left bundle branch block compared with patients with influenza without elevated hs-cTnI (*Table 2*).

A total of 50 patients were hospitalized after ED evaluation, seven (14%) patients with elevated hs-cTnI and 43 (86%) patients without elevated hs-cTnI. All patients admitted to hospital were discharged alive after a median 3 days with influenza infection (ICD code J10) as primary diagnosis. No patients needed intensive care.

Patients with influenza and elevated high-sensitivity cardiac troponin I

Seven patients hospitalized for influenza had elevated hs-cTnI; of these, two (29%) were diagnosed with influenza A and five (71%) with influenza B. Elevation of hs-cTnI was acute in five patients and

Table 1 Baseline demographic and clinical characteristics of included patients who were and were not diagnosed with influenza

	Influenza 181	No influenza 285	*P-value
Demographics			
Female, *n* (%)	86 (47.5%)	146 (51.2%)	0.434
Age, years (IQR)	55 (34–72)	61 (43–75)	**0.030**
Current infection			
Days with symptoms (IQR)	4 (3–6)	4 (2–7)	0.316
Maximal temperature, °C (±SD)	39.2 (0.7)	38.9 (1.0)	**<0.001**
Recent vaccination, *n* (%)	52/178 (29.2%)	81/284 (28.5%)	0.873
Risk factors			
BMI, kg/m^2, (IQR)	26.5 (23.5–29.6)	26.8 (24.1–30.1)	0.221
Diabetes, *n* (%)	25/181 (13.8%)	41/285 (14.4%)	0.863
Hypertension, *n* (%)	65/181 (35.9%)	113/283 (39.9%)	0.385
Hyperlipidaemia, *n* (%)	34/178 (19.1%)	56/280 (20.0%)	0.813
Smoking, *n* (%)			0.315
Never	96 (53.0%)	141 (49.5%)	
Previous	39 (21.5%)	83 (29.1%)	
Current	23 (12.7%)	32 (11.2%)	
Unknown	23 (12.7%)	29 (10.2%)	
Medical history			
Asthma	33/181 (18.2%)	45/283 (15.9%)	0.531
COPD	12/181 (6.6%)	26/283 (9.2%)	0.327
Heart failure	9/179 (5.0%)	32/284 (11.2%)	**0.021**
Myocardial infarction	14/181 (7.7%)	28/283 (9.9%)	0.429
PVD	3/181 (1.7%)	9/280 (3.2%)	0.305
Stroke	7/181 (3.9%)	18/284 (6.3%)	0.249
Laboratory findings			
Hs-cTnI men, ng/L (IQR)	5.1 (2.7–17.6)	8.9 (2.5–21.6)	0.125
Hs-cTnI women, ng/L (IQR)	3.1 (2.5–8.1)	4.5 (2.5–14.0)	0.079
Hs-cTnI, elevated (%)	11 (6.1%)	32 (11.2%)	0.061
NT-proBNP, ng/L (IQR)	156 (57–549)	259 (79–1407)	**<0.001**
NT-proBNP, elevated (%)	62/179 (34.6%)	131/282 (46.5%)	**0.012**
eGFR, mL/min/1.73 m^2 (%)	85 (63–96)	76 (60–95)	0.036
Hs-CRP mg/L (IQR)	33 (17–57)	57 (22–129)	**<0.001**
WBC, ×10*9/L (±SD)	7.2 (3.5)	10.0 (4.2)	**<0.001**
Neutrophils, ×10*9/L (±SD)	5.4 (3.5)	7.8 (4.0)	**<0.001**
Lymphocytes, ×10*9/L (±SD)	1.0 (0.5)	1.2 (0.8)	**0.006**
Platelets, ×10*9/L (±SD)	209 (72.1)	249 (98.3)	**<0.001**
ESR, mm/h (IQR)	18 (9–31)	31 (15–53)	**<0.001**
ECG at presentation			
Heart rate b/min (±SD)	91 (19)	92 (19)	0.857
Atrial fibrillation (%)	18/175 (10.3%)	33/276 (12.0%)	0.579
ST-elevation (%)	0	4/276 (1.4%)	0.161
ST-depression (%)	8/175 (4.4%)	14/276 (4.9%)	0.807
LBBB (%)	5/175 (2.8%)	8/276 (2.8%)	0.977

Elevated hs-cTnI: men ≥57 ng/L and women ≥37 ng/L. Continuous variables with missing values, number (influenza/no influenza): days with symptoms 179/285, temperature 167/265, BMI 178/280, NT-proBNP 179/282, eGFR 174/280, hs-CRP 179/285, WBW 177/282, neutrophils 132/203, lymphocytes 130/200, platelets 177/279, ESR 92/139, heart rate 175/276. BMI, body mass index; COPD, chronic obstructive pulmonary disease; ESR, erythrocyte sedimentation rate; ECG, electrocardiogram; PVD, peripheral vascular disease; Hs-CRP, high-sensitivity C-reactive protein; LBBB, left bundle branch block; WBC, white blood cells.
Bold *P*-values are significant ($P < 0.05$).
**P*-value: difference between patients with and without influenza.

Table 2 Baseline demographic and clinical characteristics of patients with influenza, stratified by high-sensitivity cardiac troponin I elevation

	Influenza		*P*-value
	Elevated hs-cTnI	No elevated hs-cTnI	
Total, *n*	11	170	
Demographics			
Female (%)	4 (36.4%)	82 (48.2%)	0.445
Age, years (±IQR)	74 (56–87)	52 (34–71)	**0.010**
Current infection			
Days with symptoms (IQR)	4 (2–5)	4 (3–6)	0.441
Recent influenza vaccination	5 (45.5%)	47 (28.1%)	0.303
Risk factors (%)			
BMI kg (±SD)	24.9 (20.8–28.2)	25.5 (23.6–29.7)	0.170
Diabetes	1 (9.1%)	24 (14.1%)	1.000
Hypertension	7 (63.6%)	58 (34.1%)	0.058
Hyperlipidaemia	4 (44.4%	30 (17.8%)	0.069
Smoking			0.719
Never	4 (36.4%)	92 (54.1%)	
Previous	3 (27.3%)	36 (21.2%)	
Current	2 (18.2%)	21 (12.4%)	
Unknown	2 (18.2%)	21 (12.4%)	
Medical history, %			
Asthma	0	33 (19.4%)	0.219
COPD	1 (9.1%)	11 (6.5%)	0.540
Heart failure	2 (18.2%)	7 (4.2%)	0.098
MI	2 (18.2%)	12 (7.1%)	0.204
PVD	1 (9.1%)	2 (1.2%)	0.172
Stroke	2 (18.2%)	5 (2.9%)	0.060
Laboratory findings			
Hs-cTnI, median, ng/L (IQR)	85.0 (62.3–252.3)	3.7 (2.5–8.7)	**<0.001**
Hs-cTnI, mean, ng/L (±SD)	132.6 (103.2)	7.6 (8.6)	**<0.001**
NT-proBNP, ng/L (IQR)	2760 (1001.8–4886.8)	143 (55.0–447.5)	**<0.001**
NT-proBNP, elevated, *n* (%)	9 (81.8%)	53 (31.2%)	**<0.001**
Hs-CRP mg/L (IQR)	50.0 (37.0–104.0)	31.5 (17.0–52.5)	**0.016**
WBC, ×10*9/L (±SD)	8.3 (3.3)	7.1 (3.5)	0.288
Platelets, ×10*9/L (±SD)	207.2 (46.7)	208.8 (73.6)	0.943
eGFR, µmol/L (IQR)	69.0 (42.0–78.0)	85.0 (65.0–96.0)	0.052
ECG at presention			
Heart rate b/min (±SD)	95 (24)	91 (18)	0.517
Atrial fibrillation (%)	2 (18.2%)	16 (9.4%)	0.300
ST-elevation (%)	0	0	0
ST-depression (%)	0	8 (4.7%)	1.00
LBBB (%)	3 (27.3%)	2 (1.2%)	**0.002**

Variable with missing values, numbers (elevated/no elevated): heart rate 0/164. BMI, body mass index; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; PVD, peripheral vascular disease; Hs-CRP, high-sensitivity C-reactive protein; WBC, white blood cells; LBBB, left bundle branch block.
Bold *P*-values are significant ($P < 0.05$).
**P*-value: difference between patients with and without elevated hs-cTnI.

suspected of being chronic in the other two, although an acute component could not be completely ruled out.

Four patients with influenza and elevated hs-cTnI at inclusion were not hospitalized, with no further assessments documented in either hospital or outpatient-clinic charts. All were men aged between 27 and 74 years, with two diagnosed with influenza A and two diagnosed with influenza B. Electrocardiograms of all four showed sinus rhythm but no evidence of pathological ST-elevation or ST-depression. However, one individual had a left branch bundle block. A review of their medical charts found no evidence that their hs-cTnI concentrations had been measured before or after the event.

Table 3 Univariate and multivariate Cox regression analyses of factors associated with major adverse cardiovascular events

Demographics			Univariate			Multivariate		
		Number	HR	95%CI	*P*-value	HR	95%CI	*P*-value
Sex	Men	95						
	Women	86	0.67	0.16–2.79	0.572			
Age		181	1.14	1.05–1.23	**<0.002**	1.13	0.98–1.29	0.085
Current infection								
Days with symptoms		181	0.93	0.72–1.21	0.585			
Recent vaccination	No	129						
	Yes	52	2.57	0.64–10.27	0.182			
Risk factors								
BMI		181	1.00	0.86–1.16	0.973			
Diabetes	No	156						
	Yes	25	0.88	0.11–7.12	0.902			
Hypertension	No	116						
	Yes	65	5.56	1.12–27.53	**0.036**	1.30	0.19–8.95	0.655
Hyperlipidaemia	No	147						
	Yes	34	1.45	0.29–7.17	0.651			
Smoking	No	119						
	Yes	62	1.14	0.27–4.78	0.856			
Medical history								
Asthma or COPD	No	142						
	Yes	39	0.03	0.00–43.83	0.354			
Heart failure	No	172						
	Yes	9	2.80	0.34–22.76	0.336			
MI	No	167						
	Yes	14	4.223	0.85–20.94	0.078			
Stroke	No	174						
	Yes	7	3.84	0.47–31.22	0.208			
Laboratory findings								
Troponin I, elevated	No	170						
	Yes	11	18.29	4.57–73.24	**<0.001**	4.96	1.10–22.41	**0.037**
Troponin I, ng/L		181	1.01	1.01–1.02	**<0.001**			
NT-proBNP, elevated	No	119						
	Yes	62	14.21	1.75–115.5	**0.013**	0.73	0.06–9.18	0.805
eGFR		181	0.94	0.91–0.97	**<0.001**	0.97	0.92–1.03	0.321
Hs-CRP mg/L		181	1.01	1.00–1.02	**0.045**	1.00	0.98–1.02	0.742
WBC, ×10*9/L		181	1.12	1.01–1.25	**0.039**	1.32	0.98–1.79	0.068
Platelets, ×10*9/L		181	1.01	1.00–1.01	0.136			
ECG at presentation								
Atrial fibrillation	No	163						
	Yes	18	3.17	0.64–15.73	0.157			
ST-depression	No	173						
	Yes	8	0.05	0.12–85.24	0.685			
LBBB	No	176						
	Yes	5	6.01	0.74–48.88	0.094			

BMI, body mass index; ECG, electrocardiogram; Hs-CRP, high-sensitivity C-reactive protein; LBBB, left bundle branch block; WBC, white blood cells.
Bold *P*-values are significant ($P < 0.05$).
*Multivariate analysis: Cox regression analysis including all factors $P < 0.05$ in the univariate analysis.

Outcome in patients with influenza

At 1-year follow-up, eight (4%) of the patients with influenza had experienced MACE; including four with (36%) and four (2%) without elevated hs-cTnI ($P < 0.01$). All four patients with influenza and elevated hs-cTnI who experienced MACE died, one of a cardiovascular cause (stroke) and three off non-cardiovascular causes (one each of ileus, acute gastric ulcer, and pulmonary cancer). Of the four patients with influenza but without elevated hs-cTnI who experienced MACE, one was later admitted with MI, one with stroke, and one with atrial fibrillation, with the fourth dying of pneumonia.

One patient each experienced MACE 11 and 44 days after being diagnosed with influenza, with the remaining events occurring 5–11 months later. No patients were lost to follow-up.

Variables associated with major adverse cardiovascular events in patients diagnosed with influenza

Univariate analysis of variables associated with MACE in patients with influenza infection was older age; hypertension; lower estimated glomerular filtration rate; higher concentrations of hs-cTnI, NT-proBNP, and hs-CRP; and higher WBC counts (*Table 3*). In multivariable analysis, elevated hs-cTnI was independently associated with MACE (*Table 3*). The association between elevated hs-cTnI and MACE was also evaluated by log-rank test and a Kaplan–Meier curve, $P < 0.001$.

Patients without influenza

The prevalence of elevated hs-cTnI was 11 and 13% experienced MACE in the non-influenza group. A total of 123 patients (44%) were hospitalized after ED evaluation, of which 25 patients had elevated hs-cTnI and 98 patients had not. Diseases of the respiratory system were the most common discharge diagnoses (56.1%), followed by diseases of the circulatory system (12.2%), diseases of the genitourinary system (11.4%), and certain infectious and parasitic diseases (10.6%). An additional 12 patients were admitted within 30 days, and their discharge diagnoses were also mainly among the diseases of respiratory system (see Supplementary material online, *Table S1*). The majority of patients without admission to hospital received unspecified diagnoses at the EDs. In univariate analysis, elevated hs-cTnI was associated with outcome: HR 3.43 (95%CI 1.653–7.119), $P < 0.001$.

Discussion

In this prospective cohort study assessing the prevalence and prognostic value of elevated hs-cTnI in an unselected population of patients with laboratory-confirmed influenza infection patients were included during three influenza seasons. The prevalence of elevated hs-cTnI in our cohort of 181 patients with documented influenza was 6%, much lower than in two recent retrospective studies, which found that the prevalence rates of elevated hs-cTn in patients with influenza were 31.8,[23] 47.7,[25] and 65.5%.[24] However, unlike the present prospective study, the two previous retrospective reports calculated the prevalence of elevated hs-cTn in selected individuals in whom hs-cTn had been measured, thus increasing the likelihood of inclusion bias. Furthermore, the median age of patients in the present study was 55 years, and most had not been admitted to hospital. By contrast, the median age of the patients in the previous studies was between 66 and 80 years, and a large proportion of patients had been admitted to hospital, implying more severe disease.[24,25] Additionally, in the recent prospective study 12.4% were admitted to the intensive care unit.[24] The prevalence rates of elevated hs-cTn patients aged ≥65 years in those admitted to hospital in the present study, however, were 10 and 14%, respectively.

During the 1-year follow-up period, 4% of the patients in this cohort experienced at least one adverse event. Half of these patients experienced a cardiovascular event (MI, stroke, atrial fibrillation, or death from stroke) and the rest died of non-cardiovascular causes. Multivariate analysis showed that elevated hs-cTnI was independently associated with MACE. However, due to the low number of events, this finding must be interpreted with caution.

Several studies have demonstrated an increased risk of cardiovascular events following infection with influenza virus.[4,5,9–15] The pathophysiological mechanisms underlying triggering of cardiovascular complications can include increased coronary and systemic inflammatory activity,[28] release of cytokines and interleukins that may lead to plaque destabilization,[28] plaque rupture,[29] increased procoagulant conditions including triggering of the coagulation cascade,[28–30] sympathetic activation with subsequent effects on vascular tone with vasoconstriction,[30] endothelial dysfunction,[28,30] and inadequate coronary artery blood flow due to increased metabolic demand, with fever, tachycardia, reduced oxygen saturation, and hypotension.[28,30]

In the present study, half of the major adverse events were cardiovascular and the rest were non-cardiovascular. Our univariate and multivariate analyses indicate that older age, elevated hs-cTnI, lower eGFR, and higher inflammatory markers to be associated with MACE. We hypothesize that an elevated hs-cTnI in an older individual during influenza infection is a sign of frailty that may serve as a prognosticator for poor prognosis.

Although none of the patients with influenza in the present study experienced myocarditis, four patients with elevated hs-cTnI at the time of study inclusion were not hospitalized and review of their inpatient and outpatient medical charts found no further assessments. All were men aged between 27 and 74 years of age; all had ECGs showing normofrequent sinus rhythm without ST-elevation or depression. However, one individual had a left branch bundle block. Thus, the mechanism underlying hs-cTnI elevation in these patients could not be determined.

The control group, consisting of patients with influenza-like symptoms but negative PCR test for influenza, had at baseline higher levels of NT-proBNP and inflammatory biomarkers compared with the influenza group. The older age and more prevalent heart failure in the control group may contribute to the difference in NT-proBNP levels. Furthermore, the control group was more often than the influenza group affected of bacterial infections resulting in pneumonia and sepsis and this may contribute to the higher levels of inflammatory markers.

Increased levels of hs-cTn hold prognostic value in hospitalized influenza patients,[24,25] in unselected patients presenting to the ED with symptoms suggestive of acute coronary syndrome[31] and inpatients at cardiac wards.[32] Patients with evidence of myocardial injury or Type

2 MI in these settings have worse short-term[31] and long-term outcomes.[32] In a recent systematic review and meta-analysis, elevated hs-cTn is a reliable predictor of cardiovascular risk in the general population and that the risk of all-cause death, cardiovascular death, and hospitalization due to heart failure increases with biomarker levels.[33]

Elevated hs-cTnI in patients with influenza in the present study was associated with adverse long-term but not short-term prognosis. This finding, contrasts observations from previous studies indicating significant short-term effects.[10,23–25] Differences in composition of cohorts, number of inpatients, and the severity of influenza disease may contribute to the discrepancy. Patients with elevated hs-cTnI were older, had more often elevated NT-proBNP and hs-CRP than patients without elevated hs-cTnI. Cardiovascular risk factors such as sex, smoking, previous cardiovascular disease, and previous heart failure were however similar between groups. This implies that elevated hs-cTnI, as a marker of myocardial injury, in patients with influenza carries an independent prognostic value.

Clinical implications

The present study found that the prevalence of elevated hs-cTnI in an unselected population with influenza infection is low. An elevated hs-cTnI accompanying influenza was associated with poor prognosis. Most of the patients with elevated hs-cTnI also needed in-hospital care. An elevated hs-cTnI in an older individual during influenza may therefore be used as a sign of frailty and poor prognosis.

Strengths and limitations

The strengths of the present study are its prospective design with patients included during three influenza seasons, the large number of patients, the broad inclusion criteria, and the use of an hs-cTn assay. The inclusion of consecutive patients makes the study more universal and the results more generalizable.

One limitation is that, for ethical reasons, the most seriously ill patients seeking care could not be included. Furthermore, patients with obvious ongoing symptoms, indicating an acute coronary syndrome, pulmonary oedema, severe arrhythmia, or acute stroke were excluded. These findings therefore represent hs-cTnI concentrations in patients with influenza-like symptoms. Furthermore, since the study had broad inclusion criteria and exclusion criteria was few, this allowed patients with another clinical conditions to be included, in whom hs-cTnI may be elevated, i.e. end stage renal disease, severe hypertension, anaemia, stress cardiomyopathy, chronic obstructive pulmonary disease, heart failure, pulmonary embolism, severe sepsis, and massive rhabdomyolysis. However, we were able to identify most of these conditions using baseline data and review of medical charts.

The event rate was low and all multivariate analyses must therefore be interpreted with caution. In our multivariable Cox regression model seven factors, univariably associated with MACE, were assessed. This may be considered too many when the number of events is small. Several different procedures, including Cox regression stepwise forward and backward analyses and log-rank test, illustrated by the Kaplan–Meier curve, were used to ascertain the results further.

The spread of COVID-19 started during the last influenza season included in the study. The first confirmed COVID-19 case in Sweden was diagnosed on 31 January 2020 according to Swedish authorities[34] and because only selected patients were tested for COVID-19 in the beginning of the pandemic, we could not determine whether some of the patients in the present study were infected with this virus. Thus, we cannot exclude the possibility that some of these patients had concurrent influenza and COVID-19 infection. However, of 54 patients included between 1 October 2019, and 17 February 2020, 13 were positive for influenza and 41 were not. High-sensitivity cTnI levels were elevated in seven patients, all negative for influenza. Hence, the association between elevated hs-cTnI and prognosis was most likely not caused by myocardial injury from COVID-19.

Our aim was to include a broad population of unselected patients with influenza-like symptoms around the clock at two hospitals. No predetermined criteria for testing were used and it was up to the physicians in charge to decide if a test for influenza was indicated or not. No screening log was used and therefore we have no information about patients not included in the study. The proportion of patients vaccinated was 29% in both patients with and without influenza. Previous influenza vaccination status did not seem to prevent from testing for influenza illness. The study may have influenced the medical staff to test more individuals for influenza than usual.

Conclusion

This study showed that in a consecutive cohort of unselected patients with influenza-like symptoms seeking medical care at Swedish emergency departments, the prevalence of elevated hs-cTnI is low. Individuals with influenza and elevated hs-cTnI seemed to have a poorer prognosis than those with influenza and non-elevated hs-cTnI.

Lead author biography

Anna M Nordenskjöld (MD, PhD) work as a senior consultant in the cardiology department at Örebro University Hospital, Sweden, and is affiliated to the Faculty of Medicine and Health, Örebro University. She is interested in a wide range of topics and have previously published studies on ischaemic heart disease, myocardial infarction with non-obstructive coronary arteries, biomarkers, and the association between affective disorder and cardiovascular disease.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

Funding

This study was supported by grants from the Region Örebro County Council Research Committee (OLL-762511, OLL-935107, OLL-939142).

Conflict of interest: O.F. has received an unrestricted research grant from Sanofi Pasteur. A.M.N., S.A., N.J., and E.S. have no conflicts of interest.

References

1. WHO. Influenza (Seasonal)- fact sheet. http://www.who.int/news-room/fact-sheets/detail/influenza-(seasonal). 2018.
2. Caforio AL, Pankuweit S, Arbustini E, Basso C, Gimeno-Blanes J, Felix SB, Fu M, Helio T, Heymans S, Jahns R, Klingel K, Linhart A, Maisch B, McKenna W, Mogensen J, Pinto YM, Ristic A, Schultheiss H-P, Seggewiss H, Tavazzi L, Thiene G, Yilmaz A, Charron P, Elliott PM. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European society of cardiology working group on myocardial and pericardial diseases. *Eur Heart J* 2013;**34**:2636–2648. 2648a–2648d.
3. Kindermann I, Barth C, Mahfoud F, Ukena C, Lenski M, Yilmaz A, Klingel K, Kandolf R, Sechtem U, Cooper LT, Böhm M. Update on myocarditis. *J Am Coll Cardiol* 2012;**59**:779–792.
4. Estabragh ZR, Mamas MA. The cardiovascular manifestations of influenza: a systematic review. *Int J Cardiol* 2013;**167**:2397–2403.
5. Chair SY, Cheng HY, Choi KC, Siow EKC, Cao X, Fung E. Influenza-associated hospitalizations and risk of subsequent heart failure hospital admissions: a 20-year territorywide registry study in Hong Kong, China. *Am J Epidemiol* 2021;**190**:779–785.
6. Chang TY, Chao TF, Liu CJ, Chen SJ, Chung FP, Liao JN, Tuan T-C, Chen T-J, Chen S-A. The association between influenza infection, vaccination, and atrial fibrillation: a nationwide case–control study. *Heart Rhythm* 2016;**13**:1189–1194.
7. Corrales-Medina VF, Suh KN, Rose G, Chirinos JA, Doucette S, Cameron DW, Fergusson DA. Cardiac complications in patients with community-acquired pneumonia: a systematic review and meta-analysis of observational studies. *PLoS Med* 2011;**8**:e1001048.
8. Blackburn R, Zhao H, Pebody R, Hayward A, Warren-Gash C. Laboratory-confirmed respiratory infections as predictors of hospital admission for myocardial infarction and stroke: time-series analysis of English data for 2004–2015. *Clin Infect Dis* 2018;**67**:8–17.
9. Kwong JC, Schwartz KL, Campitelli MA, Chung H, Crowcroft NS, Karnauchow T, Katz K, Ko DT, McGeer AJ, McNally D, Richardson DC, Rosella LC, Simor A, Smieja M, Zahariadis G, Gubbay JB. Acute myocardial infarction after laboratory-confirmed influenza infection. *N Engl J Med* 2018;**378**:345–353.
10. Ludwig A, Lucero-Obusan C, Schirmer P, Winston C, Holodniy M. Acute cardiac injury events ≤30 days after laboratory-confirmed influenza virus infection among U.S. Veterans, 2010–2012. *BMC Cardiovasc Disord* 2015;**15**:109.
11. Mohammad MA, Tham J, Koul S, Rylance R, Bergh C, Erlinge D, Fröbert O. Association of acute myocardial infarction with influenza: a nationwide observational study. *PLoS One* 2020;**15**:e0236866.
12. Warren-Gash C, Blackburn R, Whitaker H, McMenamin J, Hayward AC. Laboratory-confirmed respiratory infections as triggers for acute myocardial infarction and stroke: a self-controlled case series analysis of national linked datasets from Scotland. *Eur Respir J* 2018;**51**:1701794.
13. Warren-Gash C, Hayward AC, Hemingway H, Denaxas S, Thomas SL, Timmis AD, Whitaker H, Smeeth L. Influenza infection and risk of acute myocardial infarction in England and Wales: a CALIBER self-controlled case series study. *J Infect Dis* 2012;**206**:1652–1659.
14. Young-Xu Y, Smith J, Mahmud SM, Van Aalst R, Thommes EW, Neupane N, Lee JKH, Chit A. Laboratory-confirmed influenza infection and acute myocardial infarction among United States senior veterans. *PLoS One* 2020;**15**:e0243248.
15. Ohland J, Warren-Gash C, Blackburn R, Molbak K, Valentiner-Branth P, Nielsen J, Emborg H-D. Acute myocardial infarctions and stroke triggered by laboratory-confirmed respiratory infections in Denmark 2010 to 2016. *Euro Surveill* 2020;**25**:1900199.
16. Tripathi B, Kumar V, Kalra A, Gupta T, Sawant AC, Sharma P, Arora S, Panhwar MS, Gopalan R, Deshmukh A, Pershad A, Gulati M, Bhatt DL. Influence of influenza infection on in-hospital acute myocardial infarction outcomes. *Am J Cardiol* 2020;**130**:7–14.
17. Vejpongsa P, Kitkungvan D, Madjid M, Charitakis K, Anderson HV, Arain S, Balan P, Smalling RW, Dhoble A. Outcomes of acute myocardial infarction in patients with influenza and other viral respiratory infections. *Am J Med* 2019;**132**:1173–1181.
18. Frobert O, Gotberg M, Erlinge D, Akhtar Z, Christiansen EH, MacIntyre CR, Oldroyd KG, Motovska Z, Erglis A, Moer R, Hlinomaz O, Jakobsen L, Engstrøm T, Jensen LO, Fallesen CO, Jensen SE, Angerås O, Calais F, Kåregren A, Lauermann J, Mokhtari A, Nilsson J, Persson J, Stalby P, Islam AKMM, Rahman A, Malik F, Choudhury S, Collier T, Pocock SJ, Pernow J. Influenza vaccination after myocardial infarction: a randomized, double-blind, placebo-controlled, multicenter trial. *Circulation* 2021;**144**:1476–1484.
19. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD, Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD, Mickley H, Crea F, Van de Werf F, Bucciarelli-Ducci C, Katus HA, Pinto FJ, Antman EM, Hamm CW, De Caterina R, Januzzi JL, Apple FS, Alonso Garcia MA, Underwood SR, Canty JM, Lyon AR, Devereaux PJ, Zamorano JL, Lindahl B, Weintraub WS, Newby LK, Virmani R, Vranckx P, Cutlip D, Gibbons RJ, Smith SC, Atar D, Luepker RV, Robertson RM, Bonow RO, Steg PG, O'Gara PT, Fox KAA, Hasdai D, Aboyans V, Achenbach S, Agewall S, Alexander T, Avezum A, Barbato E, Bassand J-P, Bates E, Bittl JA, Breithardt G, Bueno H, Bugiardini R, Cohen MG, Dangas G, de Lemos JA, Delgado V, Filippatos G, Fry E, Granger CB, Halvorsen S, Hlatky MA, Ibanez B, James S, Kastrati A, Leclercq C, Mahaffey KW, Mehta L, Müller C, Patrono C, Piepoli MF, Piñeiro D, Roffi M, Rubboli A, Sharma S, Simpson IA, Tendera M, Valgimigli M, van der Wal AC, Windecker S, Chettibi M, Hayrapetyan H, Roithinger FX, Aliyev F, Sujayeva V, Claeys MJ, Smajić E, Kala P, Iversen KK, El Hefny E, Marandi T, Porela P, Antov S, Gilard M, Blankenberg S, Davlouros P, Gudnason T, Alcalai R, Colivicchi F, Elezi S, Baitova G, Zakke I, Gustiene O, Beissel J, Dingli P, Grosu A, Damman P, Juliebø V, Legutko J, Morais J, Tatu-Chitoiu G, Yakovlev A, Zavatta M, Nedeljkovic M, Radsel P, Sionis A, Jemberg T, Müller C, Abid L, Abaci A, Parkhomenko A, Corbett S. Fourth universal definition of myocardial infarction (2018). *Eur Heart J* 2019;**40**:237–269.
20. Fagnoul D, Pasquier P, Bodson L, Ortiz JA, Vincent JL, De Backer D. Myocardial dysfunction during H1N1 influenza infection. *J Crit Care* 2013;**28**:321–327.
21. Ito T, Akamatsu K, Fujita SI, Kanzaki Y, Ukimura A, Hoshiga M. Transient depression of myocardial function after influenza virus infection: a study of echocardiographic tissue imaging. *PLoS One* 2019;**14**:e0221628.
22. Lippi G, Sanchis-Gomar F. Cardiac troponin elevation in patients with influenza virus infections. *Biomed J* 2021;**44**:183–189.
23. Pizzini A, Burkert F, Theurl I, Weiss G, Bellmann-Weiler R. Prognostic impact of high sensitive troponin T in patients with influenza virus infection: a retrospective analysis. *Heart Lung* 2020;**49**:105–109.
24. Biasco L, Klersy C, Beretta GS, Valgimigli M, Valotta A, Gabutti L, Bruna RD, Pagnamenta A, Tersalvi G, Ruinelli L, Artero A, Senatore G, Jüni P, Pedrazzini GB. Comparative frequency and prognostic impact of myocardial injury in hospitalized patients with COVID-19 and influenza. *Eur Heart J Open* 2021;**1**:oeab025.
25. Sharma Y, Horwood C, Chua A, Hakendorf P, Thompson C. Prognostic impact of high sensitive troponin in predicting 30-day mortality among patients admitted to hospital with influenza. *Int J Cardiol Heart Vasc* 2021;**32**:100682.
26. Guerrisi C, Turbelin C, Blanchon T, Hanslik T, Bonmarin I, Levy-Bruhl D, Perrotta D, Paolotti D, Smallenburg R, Koppeschaar C, Franco AO, Mexia R, Edmunds WJ, Sile B, Pebody R, van Straten E, Meloni S, Moreno Y, Duggan J, Kjelsø C, Colizza V. Participatory syndromic surveillance of influenza in Europe. *J Inf Dis* 2016;**214**:S386–S392.
27. Collet JP, Thiele H, Barbato E, Barthelemy O, Bauersachs J, Bhatt DL, Dendale P, Dorobantu M, Edvardsen T, Folliguet T, Gale CP, Gilard M, Jobs A, Jüni P, Lambrinou E, Lewis BS, Mehilli J, Meliga E, Merkely B, Mueller C, Roffi M, Rutten FH, Sibbing D, Siontis GCM, ESC Scientific Document Group. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2021;**42**:1289–1367.
28. Musher DM, Abers MS, Corrales-Medina VF. Acute infection and myocardial infarction. *N Engl J Med* 2019;**380**:171–176.
29. Keller T, Weeda VB, van Dongen CJ, Levi M. Influenza vaccines for preventing coronary heart disease. *Cochrane Database Syst Rev* 2008;**3**:CD005050.
30. Corrales-Medina VF, Madjid M, Musher DM. Role of acute infection in triggering acute coronary syndromes. *Lancet Infect Dis* 2010;**10**:83–92.
31. Sandoval Y, Smith SW, Sexter A, Thordsen SE, Bruen CA, Carlson MD, Dodd KW, Driver BE, Hu Y, Jacoby K, Johnson BK, Love SA, Moore JC, Schulz K, Scott NL, Apple FS. Type 1 and 2 myocardial infarction and myocardial injury: clinical transition to high-sensitivity cardiac troponin I. *Am J Med* 2017;**130**:1431–1439.e4.
32. Chapman AR, Shah ASV, Lee KK, Anand A, Francis O, Adamson P, McAllister DA, Strachan FE, Newby DE, Mills NL. Long-term outcomes in patients with type 2 myocardial infarction and myocardial injury. *Circulation* 2018;**137**:1236–1245.
33. Aimo A, Georgiopoulos G, Panichella G, Vergaro G, Passino C, Emdin M, Clerico A. High-sensitivity troponins for outcome prediction in the general population: a systematic review and meta-analysis. *Eur J Intern Med* 2022;**98**:61–68.
34. Folkhälsomyndigheten ElfSa. The first confirmed coronavirus case in Sweden. 2020.