OBSERVATIONAL STUDY

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Critical Influenza and COVID-19—A Comparative Nationwide Case-Control Study

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IMPORTANCE: Refined knowledge of risk factors for critical influenza and COVID-19 may lead to improved understanding of pathophysiology and better pandemic preparedness.

OBJECTIVES: To compare risk-factor profiles of patients admitted to intensive care with critical influenza and COVID-19.

DESIGN, SETTING, AND PATIENTS: A nationwide retrospective matched case-control study, including all adults admitted to an ICU in Sweden with influenza or COVID-19 between 2014 and September 2020 and a matched control population (ratio 1:5, patients:controls).

MEASUREMENTS AND MAIN RESULTS: Admission to an ICU. The study included 1,873 influenza and 2,567 COVID-19 ICU patients, and 9,365 and 12,835 controls, respectively, matched on sex, age, and geographical region. Influenza patients were older and less likely male, and carried a larger burden of comorbidity and a higher Simplified Acute Physiology Score III score, whereas short-term mortalities were similar when compared to COVID-19 patients. The risk-factor profiles at ICU admission were largely comparable including socioeconomic, psychiatric, and several somatic variables. Hypertension was a strong risk factor in critical COVID-19 patients compared with influenza. Nonglucocorticoid immunosuppressive therapy was associated with critical influenza but not COVID-19. Premorbid medication with statins and renin-angiotensin-aldosterone system inhibitors reduced the risk for both conditions, the opposite was a seen for glucocorticoid medication. Notably, medication with betablockers, oral anticoagulation, and platelet inhibitors reduced the risk of critical COVID-19 but not influenza.

CONCLUSIONS: The risk-factor profiles for critical influenza and COVID-19 were largely comparable; however, some important differences were noted. Hypertension was a stronger risk factor for developing critical COVID-19, whereas the use of betablockers, oral anticoagulants, and platelet inhibitors all reduced the risk of ICU admission for COVID-19 but not influenza. Findings possibly reflected differences in pathophysiological mechanisms between these conditions.

KEY WORDS: cohort studies; COVID-19; critical care; follow-up studies; influenza; mortality

Seasonal influenza has been a well-known disease for over a century and is estimated to cause up to 650,000 deaths annually (1). The COVID-19 pandemic has, up to date, caused over 6 million fatalities (2). Both these diseases may progress to critical states necessitating intensive care admission, leading to a significant strain on healthcare resources. Better notions of risk factors for critical forms of these diseases may lead to improved knowledge of pathophysiology and better pandemic preparedness. Several studies on risk factors for critical forms of COVID-19 have been published (3, 4). It is currently not fully known to what extent these factors are specific for COVID-19 or just expressions of general vulnerability to developing critical illness in the setting of viral respiratory infection. In this nationwide case-control study, we aimed to explore and compare the

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influences of comorbidities, medication, and level of education on the risk of admission to an ICU for influenza and COVID-19.

MATERIALS AND METHODS

This study was approved by the Swedish Ethical Review Authority (approval number 2020-02544). The study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for cohort studies.

Study Design and Population

In Sweden, public healthcare, including intensive care, is tax-funded and available to all citizens and permanent residents. All have a unique personal identity number, making linkage possible between national registers with virtually no loss to follow-up. In this nationwide study, we identified all ICU patients greater than or equal to 18 years old in the Swedish Intensive Care Registry (SIR) who were admitted with influenza between 2014 and 2020 (5). We also identified all ICU patients with COVID-19 admitted from March to September 2020. All influenza and COVID-19 cases were admitted with corresponding codes according to the *International Classification of Diseases,* 10th Edition (ICD-10), in addition to a polymerase chain reaction test for the viral pathogen in question. Each influenza and COVID-19 patient was matched to five control individuals who were of the same age and sex, and who were registered in the same region at their corresponding time of ICU admission. The control individuals were extracted from the Total Population Register (6).

SIR collects individual patient data within the legal framework of the Swedish National Quality Registries. Written informed consent from each patient is not required, but patients can withdraw their data from the registry at any time. Data in SIR include baseline demographics, comorbidities, variables included in the Simplified Acute Physiology Score (SAPS III), and variables on treatments given within the ICU. Data in SIR are recorded in raw format and transferred electronically to SIR after local validation at the individual ICUs. After central validation at SIR, data entries outside prespecified limits are returned to the specific ICUs for correction before data are added to the master database. Mandatory surveillance data of influenza and COVID-19 are routinely reported in cooperation with the Public Health Agency of Sweden.

Exposures and Outcomes

Baseline characteristics were defined at the time of ICU admission and extracted from SIR. Physiologic variables were recorded within 1 hour on either side of the time of ICU admission. Information on comorbidities was obtained from the Swedish National Patient Register (7). The register includes data on in- and outpatient cares, including ICD-10 codes. Primary care is not included. Comorbidity was assessed up to 5 years prior to ICU admission and was classified in accordance with Charlson comorbidity index (CCI) (8) with the addition of hypertension, psychiatric illness, and substance abuse. We used ICD-10 groups to identify psychiatric illness (F20-F99 and F10-F14) and substance abuse (F16 and F18-F19). Data on pre-ICU medications were extracted from the National Prescribed Drug Registry (9). Data on education were extracted from the Longitudinal Integration Database for Health Insurance and Labour Market Studies (10). Level of education at the time of ICU admission was categorized as less than or equal to 9, 10–12, and greater than 12 years of schooling, respectively, the last category indicating university-level education. Information on mortality was obtained from the Swedish Cause of Death Register (11). All extracted data as specified above were extracted for cases (influenza and COVID-19) and control individuals.

Outcomes

The primary outcome was critical influenza or COVID-19 requiring ICU admission.

Statistical Analysis

Categorical data are presented as proportions and percentages. Continuous data are presented as median with interquartile ranges or mean with SD, where applicable. Associations between potential risk factors and ICU admission were estimated by conditional logistic regression and presented as odds ratios (ORs) with corresponding 95% CIs. The covariates included in the univariate model were decided a priori and were chosen based on results from previous studies and with a potential influence on the risk of critical disease. Covariates with univariate significance were included in the

multivariable models. ORs from the logistic regression models are presented to express the likelihood of being admitted to ICU. Finally, the association between potential risk factors and 30-day mortality was explored using logistic regression. All analyses were carried out for influenza and COVID-19 (and, respectively, matched controls) separately. Data were analyzed as complete cases. A two-sided *p* value of less than 0.05 was considered statistically significant. Stata/MP 14.2 (StataCorp, College Station, TX) was used for all analyses.

RESULTS

Patient Sampling

Thirty influenza and 30 COVID-19 patients (and their respective controls) were excluded due to invalid registration. Invalid registration refers to patients with a temporary personal identification number, which makes linkages with national health registries impossible. In total, 1,873 influenza patients and 2,567 COVID-19 were included with 9,365 and 12,835 controls, respectively (**Fig. 1**). Controls were drawn without resampling for the respective disease cohorts. An ICU patient included as a case in the current study could not subsequently be included as a control. However, a control individual could later be included as a case (ICU patient) in the study. In total, 36 patients occurred twice in the dataset.

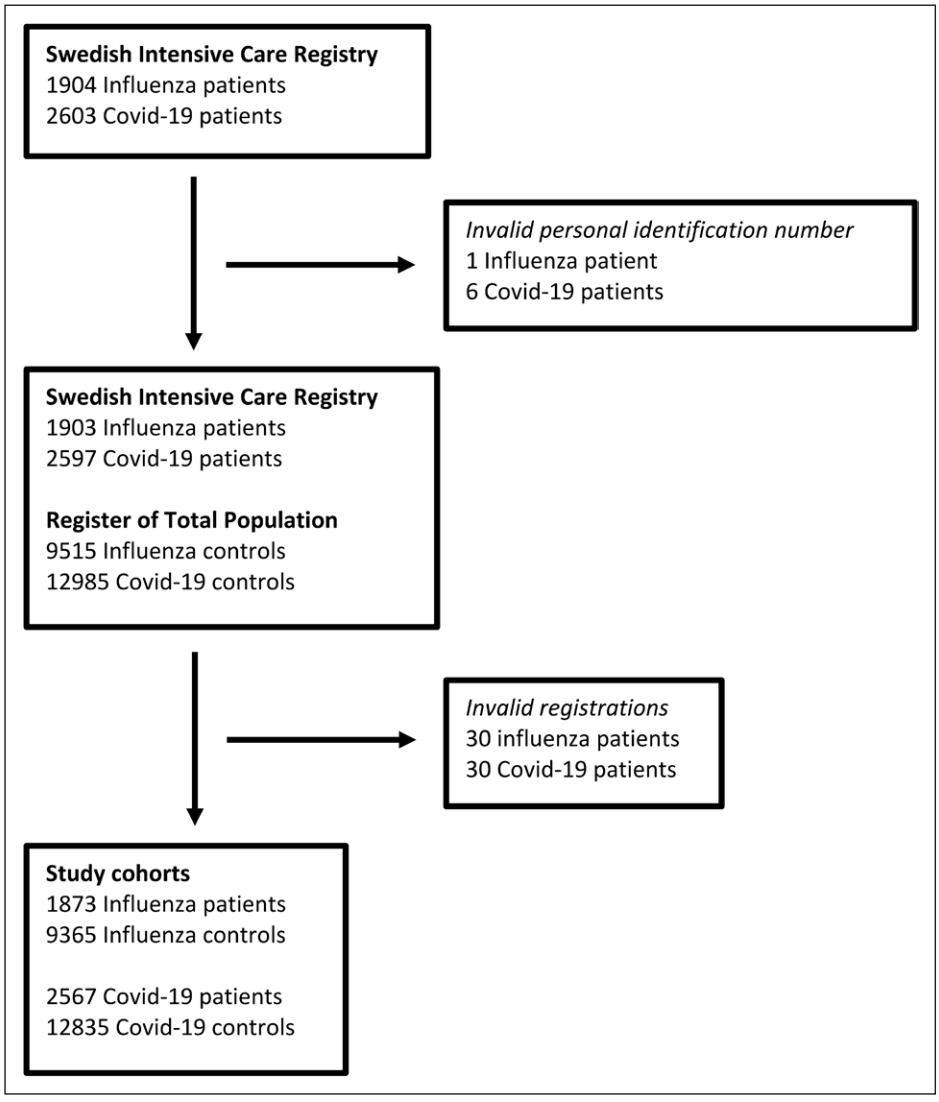

Figure 1. Flowchart of included patients and controls.

Patient Characteristics

The influenza patients were older (median age 69 vs 61) with a more balanced sex distribution (54% vs 73% male) compared with COVID-19 patients. The overall comorbidity burden was somewhat higher among influenza patients with a median CCI of 2 compared with 1 for COVID-19. The mean SAPS III score was 61 for influenza and 53 for COVID-19. At 30 days, 24% and 23% had died in the respective cohorts, and at 90 days, 29% and 28% had died (**Table 1**), respectively. Among influenza patients, 40% were admitted from emergency departments and 49% from general wards. Corresponding figures for COVID-19 patients were 25% and 71%.

Factors Associated With Critical Disease

In the multivariable conditional logistic regression analyses, the risk-factor profiles for critical disease showed great similarities between influenza and COVID-19. Hypertension, arrythmia, congestive heart failure, hemi/paraplegia, chronic obstructive pulmonary disease (COPD), diabetes, kidney disease, severe liver disease, psychiatric illness,

TABLE 1.
Demographics, Comorbidities, Premorbid Medication, and Outcomes for ICU-Admitted Influenza and COVID-19 Patients and Controls

Variable	Influenza		COVID-19	
	Controls (*n* = 9,365)	Cases (*n* = 1,873)	Controls (*n* = 12,835)	Cases (*n* = 2,567)
Age (median, IQR)	69 (56–77)	69 (56–77)	61 (52–69)	61 (52–69)
Male sex, *n* (%)	5060 (54)	1,012 (54)	9,335 (73)	1,867 (73)
Level of education, *n* (%)				
≤ 9 yr	2,448 (26)	651 (36)	2,453 (19)	653 (26)
10–12 yr	4,047 (44)	820 (45)	5,720 (45)	1,121 (45)
> 12 yr	2,780 (30)	343 (19)	4,467 (35)	700 (28)
Comorbidity				
Charlson comorbidity index, median (IQR)	0 (0–1)	2 (1–4)	0 (0–1)	1 (0–2)
Myocardial infarction, *n* (%)	461 (4.9)	292 (16)	451 (3.5)	209 (8.1)
Arrhythmia, *n* (%)	1,009 (11)	535 (29)	894 (7.0)	417 (16)
Congestive heart failure, *n* (%)	452 (4.8)	495 (26)	376 (2.9)	253 (9.9)
Hypertension, *n* (%)	2,150 (23)	943 (50)	2,124 (16)	1,239 (48)
Peripheral vascular disease, *n* (%)	268 (2.9)	143 (7.6)	238 (1.9)	93 (3.6)
Cerebrovascular disease, *n* (%)	610 (6.5)	274 (15)	472 (3.7)	219 (8.5)
Hemi/paraplegia, *n* (%)	115 (1.2)	107 (5.7)	83 (0.6)	98 (3.8)
Chronic obstructive pulmonary disease, *n* (%)	518 (5.5)	578 (31)	467 (3.6)	476 (18)
Rheumatological disease, *n* (%)	399 (4.3)	210 (11)	390 (3.0)	176 (6.9)
Diabetes, *n* (%)				
No	8,556 (91)	1,336 (71)	11,965 (93)	1,823 (71)
Without complications	560 (6.0)	317 (17)	599 (4.7)	570 (22)
With complications	249 (2.7)	220 (12)	271 (2.1)	174 (6.8)
Kidney disease, *n* (%)				
No	9,159 (98)	1,603 (86)	12,617 (98)	2,301 (90)
Moderate	202 (2.2)	239 (13)	210 (1.6)	232 (9.0)
End-stage renal disease	4 (0.0)	31 (1.7)	8 (0.1)	34 (1.3)
Liver disease, *n* (%)				
No	9,235 (99)	1,773 (95)	12,679 (99)	2,476 (96)
Mild	101 (1.1)	57 (3.0)	124 (1.0)	57 (2.2)
Moderate/severe	29 (0.3)	43 (2.3)	32 (0.2)	34 (1.3)
Malignancy, *n* (%)	1,329 (14)	357 (19)	1,255 (9.8)	262 (10)
Psychiatric illness, *n* (%)	695 (7.4)	426 (23)	919 (7.2)	381 (15)
Substance abuse, *n* (%)	215 (2.3)	160 (8.5)	316 (2.5)	109 (4.2)
Medication				
Nonsteroid immunosuppressive therapy, *n* (%)	191 (2.0)	146 (7.8)	298 (2.3)	118 (4.6)
Statins, *n* (%)	1.978 (21)	566 (30)	2.605 (20)	714 (28)

(*Continued*)

TABLE 1. (*Continued*).
Demographics, Comorbidities, Premorbid Medication, and Outcomes for ICU-Admitted Influenza and COVID-19 Patients and Controls

Variable	Influenza		COVID-19	
	Controls (*n* = 9,365)	Cases (*n* = 1,873)	Controls (*n* = 12,835)	Cases (*n* = 2,567)
Steroids, *n* (%)	497 (5.3)	396 (21)	552 (4.3)	284 (11)
Renin-angiotensin-aldosterone system inhibitors, *n* (%)	2,707 (29)	713 (38)	3,711 (29)	940 (37)
Betablockade, *n* (%)	2,044 (21.8)	720 (38)	2,137 (17)	621 (24)
Oral anticoagulants, *n* (%)	717 (7.7)	310 (17)	762 (5.9)	215 (8.4)
Platelet inhibitors, *n* (%)	1,353 (14)	444 (24)	1,435 (11)	382 (15)
Scoring and outcomes				
Simplified Acute Physiology Score III, median (IQR)		61 (53–71)		53 (47–60)
30-d mortality, *n* (%)	21 (0.2)	459 (24)	20 (0.2)	594 (23)
90-d mortality, *n* (%)	73 (0.8)	544 (29)	33 (0.3)	689 (28)

IQR = interquartile range.

and baseline medication with glucocorticoids were all associated with ICU admission in both diseases. A high level of education and baseline medication with statins as well as renin-angiotensin-aldosterone system (RAAS) inhibitors reduced the risk for critical disease in both cohorts. Substance abuse and nonsteroid immunosuppressive therapy proved to be risk factors for critical influenza but not COVID-19, whereas the opposite was noted for myocardial infarction and rheumatological disease. ß-blockers, oral anticoagulants, and platelet inhibitors were associated with a reduced risk of ICU admission due to COVID-19 but not influenza (**Tables 2** and **3**; **Fig. 2**; and **Supplemental Table 1**, http://links.lww.com/CCX/B2).

DISCUSSION

To date, several studies have compared COVID-19 with seasonal influenza from different perspectives (12, 13). To the best of our knowledge, this is the first comparative case-control study of the critical forms of these conditions. In this nationwide study, patients admitted to an ICU in Sweden with influenza were older and less likely to be male, carried a greater burden of comorbidity, and had a higher SAPS III score compared with patients admitted to ICU with COVID-19. Despite this, the short-term mortality was comparable. In the analyses of risk-factor profiles, we noted several similarities that possibly reflect a general vulnerability to severe infection. Notably, premorbid use of RAAS inhibitor and statin medication was associated with a reduced risk of ICU admission for both diseases. Some important differences were observed between the influenza and COVID-19 cohorts. The use of ß-blockers, oral anticoagulants, and platelet inhibitors was associated with a reduced risk for critical COVID-19; this association was not seen in influenza.

Some differences in demography were noted. The higher age and burden of comorbidity seen among influenza compared with COVID-19 patients have been reported previously (13, 14). A sex-related difference was noted where almost three-quarters of the COVID-19 patients were male. This difference has also been reported in several studies (3, 4). In Sweden, more females have tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) than men, but there is a clear male predominance when it comes to critical forms of disease (15). This observation has been suggested to relate to sex-related differences in the RAAS, specifically differences in the expression of angiotensin-converting enzyme 2 (ACE_2), the port of entry for SARS-CoV-2 virus (16).

Influenza patients were older and had a higher CCI and SAPS III score but a comparable short-term mortality. Similar results have been reported previously (12). Cardiovascular disease is a condition known to increase the risk of adverse outcomes in several settings. Hypertension has been shown to be a risk factor for

TABLE 2.
Influenza Patients

Variable	Univariate		Multivariable	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Level of education				
≤ 9 yr	Ref		Ref	
10–12 yr	0.73 (0.65–0.82)	0.000	0.81 (0.70–0.94)	0.006
> 12 yr	0.43 (0.37–0.50)	0.000	0.60 (0.50–0.72)	0.000
Comorbidity				
Myocardial infarction	3.8 (3.2–4.5)	0.000	1.1 (0.91–1.4)	0.302
Arrhythmia	4.1 (3.6–4.7)	0.000	2.0 (1.6–2.5)	0.000
Hypertension	4.3 (3.8–4.9)	0.000	2.1 (1.8–2.5)	0.000
Congestive heart failure	8.5 (7.2–9.9)	0.000	3.3 (2.6–4.0)	0.000
Peripheral vascular disease	2.9 (2.3–3.5)	0.000	0.91 (0.68–1.2)	0.522
Cerebrovascular disease	2.6 (2.2–3.0)	0.000	1.1 (0.90–1.4)	0.334
Hemi/paraplegia	4.9 (3.8–6.5)	0.000	3.4 (2.4–4.9)	0.000
Chronic obstructive pulmonary disease	8.0 (6.9–9.2)	0.000	4.5 (3.8–5.4)	0.000
Rheumatological disease	2.9 (2.4–3.5)	0.000	1.0 (0.78–1.3)	0.995
Diabetes				
No	Ref		Ref	
Without complications	3.9 (3.3–4.5)	0.000	2.4 (1.9–2.9)	0.000
With complications	6.2 (5.1–7.5)	0.000	3.0 (2.3–4.0)	0.000
Kidney disease				
No	Ref		Ref	
Moderate	7.4 (6.0–9.0)	0.000	2.3 (1.7–2.9)	0.000
End-stage renal disease	43 (15–121)	0.000	7.1 (2.3–22.3)	0.001
Liver disease				
No	Ref		Ref	
Mild	2.9 (2.1–4.1)	0.000	1.3 (0.85–2.1)	0.219
Moderate/severe	7.6 (4.7–12)	0.000	3.1 (1.6–5.8)	0.000
Malignancy	1.5 (1.3–1.7)	0.000	1.0 (0.88–1.3)	0.599
Psychiatric illness	3.8 (3.3–4.3)	0.000	2.4 (2.0–2.9)	0.000
Substance abuse	4.1 (3.3–5.0)	0.000	1.8 (1.4–2.4)	0.000
Medication				
Nonsteroid immunosuppressive therapy	4.2 (3.3–5.2)	0.000	2.5 (1.8–3.5)	0.000
Statins	1.7 (1.5–1.9)	0.000	0.74 (0.62–0.89)	0.002
Steroids	5.0 (4.3–5.8)	0.000	2.3 (1.9–2.8)	0.000
Renin-angiotensin-aldosterone system inhibitors	1.6 (1.4–1.8)	0.000	0.69 (0.58–0.81)	0.000
Betablockade	2.5 (2.3–2.9)	0.000	0.98 (0.82–1.2)	0.783
Oral anticoagulants	2.7 (2.3–3.1)	0.000	1.0 (0.78–1.29)	0.959
Platelet inhibitors	2.0 (1.7–2.3)	0.000	1.2 (0.97–1.5)	0.088

OR = odds ratio, Ref = reference.

Univariate and multivariable logistic regression, associations with ICU admission and presented as odds ratios.

TABLE 3.
COVID-19 Patients

Variable	Univariate		Multivariable	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Level of education				
≤ 9 yr	Ref		Ref	
10–12 yr	0.81 (0.70–0.94)	0.006	0.75 (0.66–0.86)	0.000
> 12 yr	0.60 (0.50–0.72)	0.000	0.70 (0.61–0.81)	0.000
Comorbidity				
Myocardial infarction	1.1 (0.91–1.4)	0.302	1.3 (1.1–1.7)	0.018
Arrhythmia	2.0 (1.6–2.5)	0.000	2.0 (1.7–2.5)	0.000
Hypertension	2.1 (1.8–2.5)	0.000	4.8 (4.2–5.6)	0.000
Congestive heart failure	3.3 (2.6–4.0)	0.000	1.5 (1.2–2.0)	0.001
Peripheral vascular disease	0.91 (0.68–1.2)	0.522	0.94 (0.69–1.3)	0.695
Cerebrovascular disease	1.1 (0.90–1.4)	0.334	1.1 (0.90–1.4)	0.279
Hemi/paraplegia	3.4 (2.4–4.9)	0.000	3.4 (2.3–5.0)	0.000
Chronic obstructive pulmonary disease	4.5 (3.8–5.4)	0.000	4.4 (3.7–5.2)	0.000
Rheumatological disease	1.0 (0.78–1.3)	0.995	1.4 (1.1–1.8)	0.009
Diabetes				
No	Ref		Ref	
Without complications	2.4 (1.9–2.9)	0.000	4.5 (3.8–5.3)	0.000
With complications	3.0 (2.3–4.0)	0.000	2.1 (1.6–2.8)	0.000
Kidney disease				
No	Ref		Ref	
Moderate	2.3 (1.7–2.9)	0.000	2.9 (2.2–3.7)	0.000
End-stage renal disease	7.1 (2.3–22.3)	0.001	10.7 (4.0–28.7)	0.000
Liver disease				
No	Ref		Ref	
Mild	1.3 (0.85–2.1)	0.219	0.86 (0.56–1.3)	0.477
Moderate/severe	3.1 (1.6–5.8)	0.000	1.9 (1.0–3.5)	0.036
Malignancy	1.0 (0.88–1.3)	0.599		
Psychiatric illness	2.4 (2.0–2.9)	0.000	1.7 (1.4–1.9)	0.000
Substance abuse	1.8 (1.4–2.4)	0.000	0.86 (0.65–1.1)	0.280
Medication				
Nonsteroid immunosuppressive therapy	2.5 (1.8–3.5)	0.000	1.2 (0.86–1.6)	0.334
Statins	0.74 (0.62–0.89)	0.002	0.74 (0.63–0.86)	0.000
Steroids	2.3 (1.9–2.8)	0.000	1.5 (1.2–1.8)	0.000
Renin-angiotensin-aldosterone system inhibitors	0.69 (0.58–0.81)	0.000	0.58 (0.50–0.67)	0.000
Betablockade	0.98 (0.82–1.2)	0.783	0.76 (0.64–0.89)	0.001
Oral anticoagulants	1.0 (0.78–1.29)	0.959	0.50 (0.39–0.65)	0.000
Platelet inhibitors	1.2 (0.97–1.5)	0.088	0.72 (0.59–0.88)	0.002

OR = odds ratio, Ref = reference.
Univariate and multivariable logistic regression, associations with ICU admission and presented as odds ratios.

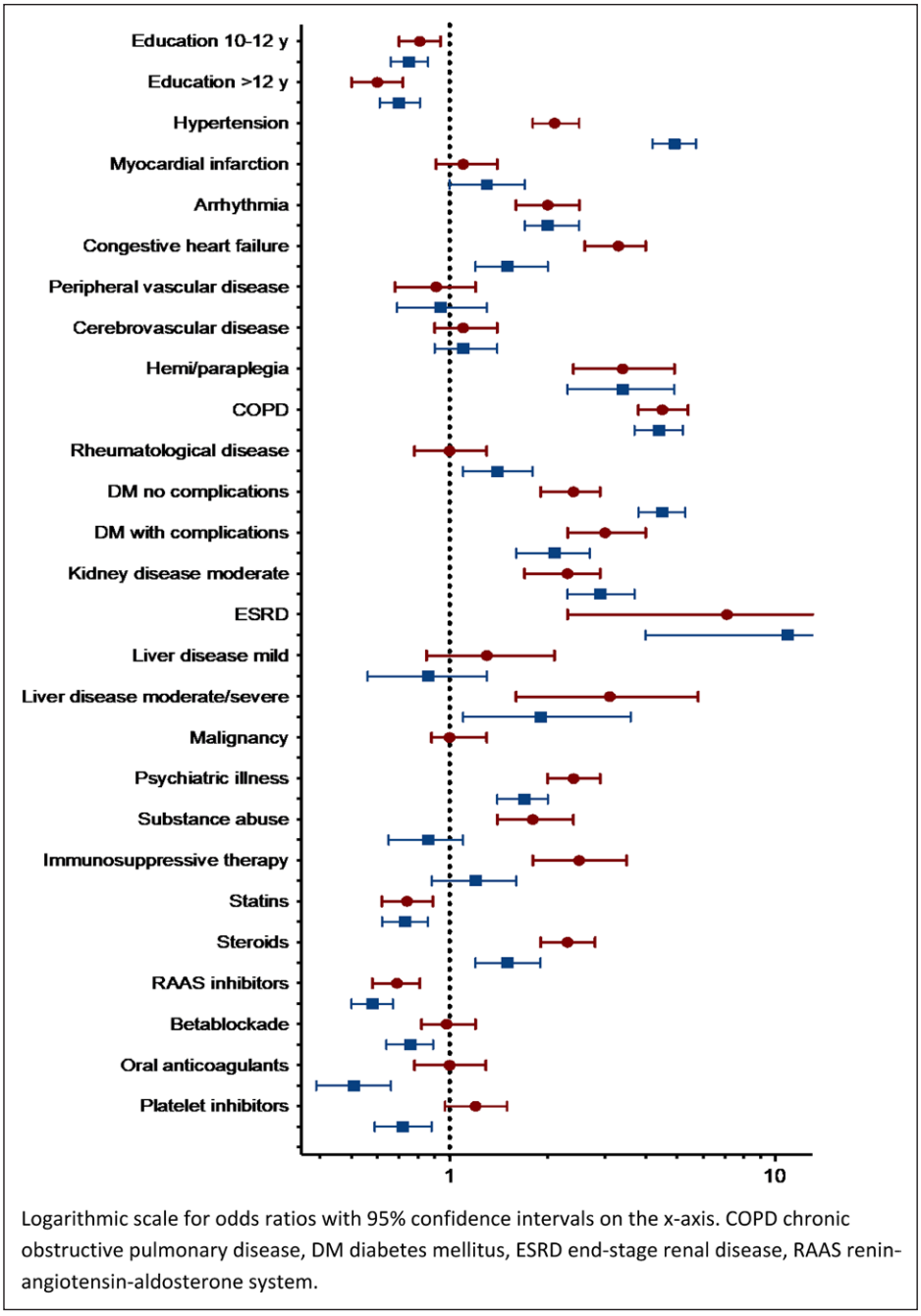

Figure 2. Multivariable logistic regression analysis of risk factors for critical influenza (*red dots*) and critical COVID-19 (*blue squares*). Logarithmic scale for odds ratios with 95% CIs on the *x*-axis. COPD = chronic obstructive pulmonary disease, DM = diabetes mellitus, ESRD = end-stage renal disease, RAAS = renin-angiotensin-aldosterone system.

severe forms of COVID-19 (4, 17). In line with these findings, hypertension proved to be associated with COVID-19 and, to a lesser extent, with influenza in the current study. Hypertension has previously been reported as a risk factor also related to other coronaviruses such as SARS and Middle East respiratory syndrome (18). The explanatory mechanisms behind these observations are not fully elucidated, but it has been suggested that this may be related to RAAS and possibly altered expression of ACE_2 (19). Congestive heart failure has been shown to increase the risk of ICU admission in community-acquired sepsis (20). This was also seen with influenza and, to a lesser degree, COVID-19 in this study. COPD proved to be a strong risk factor related to both conditions, in keeping with previous reports (21, 22).

Rheumatological disease and immunosuppressive therapy are to some extent related entities. We found that the former increased the risk of critical COVID-19 but not influenza, whereas the opposite was noted for nonglucocorticoid immunosuppressive therapy. In line with our study, a recent meta-analysis reported that the risk of developing COVID-19 was not significantly higher among immunosuppressed patients compared with the general community (23). No data on the outcomes of patients contracting COVID-19 were reported in this study. Moreover, a report from the COVID-19 Global Rheumatology Alliance showed that patients with rheumatological diseases treated with glucocorticoids had a higher risk of hospitalization for COVID-19, whereas patients on anticytokine treatment had a lower risk (24). Severe COVID-19 has been advocated as a hyperinflammatory condition, and anticytokine treatment is currently used for selected cases in the ICU. It might be that preemptive anticytokine treatment reduces the risk of severe COVID-19. As previously shown (21), immunosuppression increased the risk of critical influenza in this study. This condition involves a secondary bacterial

infection in up to 30% of the cases (25), a complication expected to increase with a reduced immune defense. Preadmission glucocorticoid medication increased the risk of contracting either condition. This has previously been reported for both influenza (26) and COVID-19 (24, 27). Interestingly, inhospital treatment with glucocorticoids in influenza-induced acute respiratory distress syndrome (ARDS) has been shown to increase mortality (28), whereas it is has been shown to decrease mortality in critical COVID-19 (29). This discrepancy may have to do with hyperinflammation in the latter and a relatively high presence of secondary bacterial infections in the former.

Diabetes is commonly reported as a risk factor for both COVID-19 (12) and influenza (30), as well as sepsis (20). Glucose variability has been associated with severity of influenza (31) in experimental models, and it has been proposed that diabetes causes a functional immune deficiency reducing immune cell function (32). An increased expression of ACE_2 patients with type 2 diabetes has been suggested as a mechanism for the development of severe COVID-19, as these receptors in the lungs and other tissues have been shown to play a role in infection with SARS-CoV-2 (33). These findings are in keeping with the current study, where diabetes was a significant risk factor for both conditions. End-stage renal disease, comprising a small group of patients, proved to be the strongest risk factor for ICU admission for both conditions. This notion is well-recognized in the literature (34, 35). Severe liver disease is a serious condition with a reduced life expectancy and is associated with immune deficiency. In line with our findings, severe liver disease has previously been reported to be associated with a several-fold increase in mortality in both COVID-19 (36) and influenza (37). Malignancy was not associated with ICU admission for influenza or COVID-19 in our study. Cancer has been reported to be associated with an increased risk of influenza complications (38), whereas the findings for COVID-19 are less consistent. In line with our finding, a matched cohort study (39) from New York reported no association between cancer and severe outcomes from COVID-19, whereas a Chinese study (40) reported an increased risk. A possible admission bias for patients with advanced malignancy cannot be fully ruled out in our study.

Socioeconomic status and psychiatric illness are reported to be associated with adverse outcomes in numerous medical conditions (20), including our study. Substance abuse proved to be a risk factor for influenza but not for COVID-19. This finding is not consistent with previous reports where substance abuse disorders are reported as risk factors for severe infections (20) including COVID-19 (41).

Statins have been advocated as potentially beneficial to critical illness due to their anti-inflammatory properties. However, recent studies do not support the use of statins in sepsis (42) or ARDS (43). Notably, these drugs may exhibit antiviral effects, and in line with the findings of the current study, premorbid statin use has been shown to reduce the risk of critical disease in both influenza (44) and COVID-19 (45).

During the initial phase of the COVID-19 pandemic, potential harm from RAAS inhibitors was discussed as these drugs may increase the expression of angiotensin-converting enzyme receptors, a port of entry for the SARS-CoV-2 virus. With increased knowledge of the role of the RAAS system in the pathophysiology of COVID-19, RAAS inhibitors were later advocated as potentially beneficial (46) and suggested as a line of treatment. A recent South American Randomized Controlled Trial (RCT) (47) showed improved survival from telmisartan treatment in hospitalized COVID-19 patients, whereas no effect was seen from losartan treatment in an American study (48). In keeping with our findings, baseline use of RAAS inhibitors has been associated with a reduced risk of adverse outcomes in both influenza (49) and COVID-19 (46).

Use of β-blockers was associated with a reduced risk of critical COVID-19 but not influenza in our study. Premorbid use of β-blockers has been associated with improved outcomes in sepsis (50), and recently, a small randomized study showed that inhospital treatment with metoprolol improved gas exchange in COVID-19–induced ARDS (51).

A hallmark of critical COVID-19 is thrombogenicity, in particular pulmonary embolism, that has been reported to occur in a third of ICU patients (52). These are typically located in the segmental arteries as well as the microcirculation and possibly generated in situ rather than embolized. Furthermore, the occurrence rate has been shown to be approximately three-fold higher in ICU-admitted COVID-19 patients compared with influenza and ICU patients in general (53).

Premorbid use of oral anticoagulants was associated with a reduction in the risk of critical COVID-19 but not influenza in our study. With some exceptions (54), this association has not been noted for COVID-19 in previous studies (27, 55, 56), and a recent RCT failed to show

any protective effects from oral anticoagulation initiated in stable outpatients with symptomatic COVID-19 (57). Antiplatelet therapy may have beneficial effects in severe COVID-19 through several mechanisms including inhibition of platelet aggregation, reduction of platelet-derived inflammation, blocking thrombogenic neutrophil extracellular traps, and reducing disseminated intravascular coagulation. Low-dose aspirin has been used as a line of therapy, and several observational studies have reported that aspirin is associated with a reduced risk of adverse outcome in COVID-19 (58, 59). In line with oral anticoagulants, premorbid treatment with platelet inhibitors was associated with a reduction in the risk of contracting critical COVID-19 but not influenza in our study. Recently, a large RCT failed to show any effect on 28-day survival but reported a significantly shorter period to discharge in aspirin-treated hospitalized COVID-19 patients (60).

Our study suggests that several preexisting medical conditions known to increase the general risk of critical illness also increase the risk for the two studied conditions. Hypertension proved to be a strong risk factor for critical COVID-19, possibly suggesting involvement of the RAAS in the pathophysiology. Likewise, premorbid RAAS inhibition was associated with a lower risk of critical disease due to COVID-19. This latter association was also seen for critical influenza. The significant risk reduction seen in patients with anticoagulant and platelet inhibitor medication in COVID-19 but not influenza suggests that thromboembolism is an important component in the development of critical forms of the former viral disease.

As with all registry-based studies, this study has limitations. The COVID-19 patients were sampled during the first pandemic wave, and the results may not be generalizable to later waves. Despite a certain preparedness and a rapid increase in ICU beds following initial reports from Italy and China, ICU capacity was obviously strained during the first wave of the pandemic. Thus, a possible admission bias between the two cohorts cannot be fully ruled out. Whether or not the pandemic affected thresholds for ICU admission has been a subject of debate and previous studies are few. Variations in ICU threshold in terms of age and comorbidities could theoretically affect the results, but unfortunately, the data set does not allow analyses of that question. In addition, data on ICU staffing and hospital care given before ICU admission would have added value. Data on ethnic or racial diversity among the study population were not available. During the pandemic, there has been a rapid increase in knowledge of optimal treatment of COVID-19. Clinical management algorithms are constantly evolving including early treatment measures to prevent disease progression. For example, inhospital treatment with dexamethasone or low-molecular-weight heparins preceding or during intensive care are not included in SIR. COVID-19 vaccines were not yet available during the inclusion period, and data on vaccination status for influenza patients are not available in the current study.

Strengths of the study include the use of validated national quality and health registers with a low rate of missing data and minimal loss to follow-up (**Supplemental Table 2**, http://links.lww.com/CCX/B3). Data are prospectively reported to SIR for quality-surveillance purposes and are, therefore, unbiased in relation to this study. All influenza and COVID-19 ICU patients in Sweden are included in the study, providing high generalizability to similar healthcare systems.

CONCLUSIONS

In this nationwide case-control study, we compared the pattern of risk factors for contracting critical influenza and COVID-19. Similarities were noted in that several significant preexisting medical conditions commonly reported as risk factors associated with critical illness proved to be risk factors also in these two conditions. Premorbid use of both statins and RAAS inhibitors was associated with a reduced risk of contracting critical forms of both conditions, whereas ß-blockers, oral anticoagulants, and platelet inhibitors only reduced the risk of critical COVID-19. The latter findings possibly reflect an important role of thromboembolism in the pathophysiology of critical COVID-19.

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