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Influenza Season and Outcome After Elective Cardiac Surgery: An Observational Cohort Study

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ABSTRACT

BACKGROUND An asymptomatic respiratory viral infection during cardiac surgery could lead to pulmonary complications and increased mortality. For elective surgery, testing for respiratory viral infection before surgery or vaccination could reduce the number of these pulmonary complications. The aim of this study was to investigate the association between influenzalike illness (ILI) seasons and prolonged mechanical ventilation and inhospital mortality in a Dutch cohort of adult elective cardiac surgery patients.

METHODS Cardiac surgery patients who were admitted to the intensive care unit between January 1, 2014, and February 1, 2020, were included. The primary endpoint was the duration of invasive mechanical ventilation in the ILI season compared with baseline season. Secondary endpoints were the median Pa_{O_2} to fraction of inspired oxygen ratio on days 1, 3, and 7 and postoperative inhospital mortality.

RESULTS A total of 42,277 patients underwent cardiac surgery, 12,994 (30.7%) in the ILI season, 15,843 (37.5%) in the intermediate season, and 13,440 (31.8%) in the baseline season. No hazard rates indicative of a longer duration of invasive mechanical ventilation during the ILI season were found. No differences were found for the median Pa_{O_2} to fraction of inspired oxygen ratio between seasons. However, inhospital mortality was higher in the ILI season compared with baseline season (odds ratio 1.67; 95% CI, 1.14-2.46).

CONCLUSIONS Patients undergoing cardiac surgery during the ILI season were at increased risk of inhospital mortality compared with patients in the baseline season. No evidence was found that this difference is caused by direct postoperative pulmonary complications.

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Pulmonary complications, such as pneumonia, pulmonary edema, and acute respiratory distress syndrome (ARDS), are currently reported as the main cause of mortality after cardiac surgery.[1] Pneumonia is common, occurring in approximately 6% of cardiac surgery patients and contributing significantly to morbidity and mortality.[2] Cardiogenic pulmonary edema is one of the leading causes of prolonged invasive mechanical ventilation (IMV) after cardiac surgery.[1] One of the most severe pulmonary complications is ARDS, a life-threatening pulmonary inflammatory response. Mortality of ARDS after cardiac surgery varies among studies, from 15% to 80%, with

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Abbreviations and Acronyms

APACHE = Acute Physiology and Chronic Health Evaluation
ARDS = acute respiratory distress syndrome
CABG = coronary artery bypass graft surgery
HR = hazard ratio
ICU = intensive care unit
ILI = influenzalike illness
IMV = invasive mechanical ventilation
NICE = National Intensive Care Evaluation
P/F = Pa_{O_2} to fraction of inspired oxygen ratio

ARDS mortality in the general population estimated at less than 40%.[3,4]

There are many risk factors for the development of pulmonary complications after cardiac surgery, not all of which can be easily influenced.[1] Examples are genetics, age, smoking status, comorbidities, and use and duration of cardiopulmonary bypass.[1]

Another risk factor is the season in which cardiac surgery is performed. Earlier research found a higher prevalence of ARDS and a longer duration of IMV among patients who underwent cardiac surgery during the influenzalike illness (ILI) season compared with a period with lower incidence of ILI.[5] In the Northern hemisphere, the ILI season typically is a period between October and April, lasting 15 weeks on average but with differences between the years.[6] A possible explanation for these results could be that an asymptomatic or presymptomatic influenza, or other respiratory viral infection, is a risk factor for pulmonary complications after cardiac surgery.[5] Many common respiratory viral infections can be asymptomatic—estimates are that more than 75% of influenza infections are asymptomatic.[7] Other, noninfluenza respiratory viruses, such as respiratory syncytial virus and adenovirus, are the cause of a substantial part of ILI and could also be risk factors.[8] Respiratory viral infections can lead to lung inflammation and epithelial damage.[9] The damaged airways increase the risk of more severe postoperative pulmonary complications, such as pneumonia or ARDS.[9] A cytokine response to viral respiratory infection can already be seen in the presymptomatic phase, and this inflammatory response could prime the lungs for more severe pulmonary problems, with cardiac surgery acting as a second hit.[10]

Another study has found higher mortality after cardiac surgery in the winter months.[11] If an asymptomatic or presymptomatic respiratory viral infection is a risk factor for pulmonary complications after cardiac surgery, testing for a viral infection or (influenza) vaccination before elective surgery could reduce the number of these complications.

We hypothesized that undergoing cardiac surgery during ILI season increases the probability of the development of postoperative pulmonary complications, such as pneumonia or ARDS, prolonging the duration of mechanical ventilation and increasing mortality. The aim of this study was to investigate the association between ILI season and a season with very low prevalence of ILI, and prolonged mechanical ventilation and inhospital mortality in a Dutch cohort of adult cardiac surgery patients.

PATIENTS AND METHODS

STUDY DESIGN AND STUDY POPULATION. In this observational cohort study, all consecutive patients who underwent elective cardiac surgery and were subsequently admitted to intensive care between January 1, 2014, and February 1, 2020, from the National Intensive Care Evaluation (NICE) database were included. The NICE database is a national database, and all 16 hospitals that perform cardiac surgery in the Netherlands upload data to the NICE database. Details were described previously.[12] From those 16 hospitals, three had a period of 2 years each in which they did not supply data on the duration of mechanical ventilation, and these periods were excluded from the analysis. Subjects less than 18 years of age were excluded.

The different types of surgery included in this study were aortic valve surgery (including transcatheter aortic valve replacement); coronary artery bypass graft; coronary artery bypass graft and single valve (replacement or repair); coronary artery bypass graft and two valves (replacement or repair); congenital defect repair; mitral valve surgery; pericardiectomy; pulmonary valve surgery; tricuspid valve surgery; and other cardiovascular surgery (not otherwise specified). Details on data collection, calculation of Age, Creatinine, and Ejection Fraction II risk score, intensive care unit (ICU) occupancy rate, and data availability can be found in the Supplemental Material.

DEFINITION OF INFLUENZA SEASON. The ILI season at the time of ICU admission was used as a proxy for risk of respiratory viral infection. The dates and duration of the national ILI season were determined using publicly available data from the Netherlands Institute for Health Services Research, which collects data from general practitioners.[13] The epidemic threshold is determined each ILI season. For the years used in this study, to and including the ILI season of 2018-2019, the epidemic threshold was set at 51 per 100,000 persons presenting with ILI for 2 consecutive weeks. From the ILI season of 2019-2020 onward, the epidemic threshold was set at an incidence 58 per 100,000 persons presenting with ILI. All patients who underwent surgery in the weeks in which the epidemic threshold was met were included in the ILI season group. Similar to previous studies,[5] a threshold of 25 or less per 100,000 persons presenting with ILI was set for the baseline season. Weeks in which the incidence was between 25 and the epidemic threshold were set as an intermediate season. The ILI season ended when the number of people presenting with ILI was lower than the epidemic threshold for 2 consecutive weeks. To have the biggest contrast in the number of respiratory viral infections between groups, ILI season and baseline season were compared. As these numbers consist of people presenting with ILI to their general practitioner, the absolute number of cases in the general population is likely to be higher.

PRIMARY AND SECONDARY OUTCOMES. The primary outcome was duration of mechanical ventilation (hours). Secondary outcomes were differences in the inhospital mortality in median Pa_{O_2} to fraction of inspired oxygen (P/F) ratio on day 1, day 3, and day 7 after surgery in the ILI season vs baseline season. The P/F ratios were not available after discharge from the ICU. An analysis including the intermediate season was performed. Only the first episode of mechanical ventilation was studied.

STATISTICAL ANALYSIS. Median and interquartile range were used to describe continuous variables, and differences between seasons were compared using the Mann-Whitney *U* test for two groups and the Kruskal- Wallis test for more than two groups. The χ^2 test was used for categoric variables. A *P* value of less than .05 was considered to indicate statistical significance. Multiple comparisons were adjusted using the Bonferroni method. Records with missing data were excluded from the analysis. Statistical analysis was performed using R 4.0.3 statistical software (R Foundation for Statistical Computing).

Clinically relevant variables were included as predictors in the multivariable analysis: ILI season; year of surgery; age; sex; body mass index; Acute Physiology and Chronic Health Evaluation IV (APACHE IV) predicted mortality;[14] type of surgery; Charlson comorbidity index; Age, Creatinine, and Ejection Fraction II risk score; hospital type; and ICU occupancy rate. Because congestive heart failure is part of the Charlson comorbidity index, New York Heart Association class IV was not included separately.

For the duration of mechanical ventilation, a Cox regression analysis was done, with extubation as the event of interest. Higher rates of extubation necessarily imply shorter duration of ventilation, albeit this duration is not the explicit outcome in a Cox model. The proportional hazards assumption for ILI season was checked by visual inspection and including an interaction term for ILI season and duration of mechanical ventilation. The duration of mechanical ventilation was censured at the time of death for patients who died inhospital, if they died while receiving IMV. Because the severity of influenza seasons differs per year, we compared each ILI season with the baseline season in the same year. To do so, terms for the interaction between the year in which surgery was performed (eg, 2014-2015) and the season in which surgery was performed (baseline/ILI) were included in the Cox regression model. This way, for every ILI season, the effect on our primary endpoint (duration of mechanical ventilation, in hours) could be calculated, compared with baseline season of that same year.

The Cox regression model results in a hazard ratio, expressing the hazard of stopping IMV in the ILI season divided by the hazard of stopping IMV in the baseline season. The proportional hazards assumption was tested using residual plots. For inhospital mortality, a logistic regression analysis was performed. Finally, for the P/F ratios on day 1, 3, and 7, linear regression analyses were performed. Differences in APACHE IV predicted mortality reflect the severity of illness after surgery as it is measured at the start of ICU admission. However, following the hypothesis that a viral respiratory infection at the time of surgery leads to worse outcomes, it could be that the APACHE IV predicted mortality is influenced by a process that started earlier and is exacerbated by the surgery. Therefore, a sensitivity analysis excluding the APACHE IV predicted mortality as a predictor was performed.

ETHICAL APPROVAL. Per Dutch legislation, approval from an Ethical Committee is not required for large register-based studies with routinely collected health care data, provided the results cannot be traced to an individual. However, hospitals consented to their data being used for this analysis.

RESULTS

BASELINE CHARACTERISTICS. Between January 1, 2014, and February 1, 2020, a total of 42,277 adult patients underwent elective cardiac surgery, 12,994 (30.7%) in the ILI season, 13,440 (31.8%) in the baseline season, and 15,843 (37.5%) in the intermediate season. There were no patients with missing data for the primary outcome and few with missing data for the secondary outcomes (ie, inhospital mortality, 0%; P/F day 1, 4%; P/F day 3, 1.5%; and P/F day 7, 0.6%). During our study period, 130 weeks were defined as baseline season, 129 weeks were defined as intermediate season, and 114 weeks were in the ILI season. On average, 103 surgeries were performed each week during baseline season, 123 surgeries per week during intermediate season, and 114 surgeries each week during ILI season.

Table 1 shows the demographics for patients who underwent surgery in baseline season compared with

TABLE 1 Clinical Characteristics of Patients Who Underwent Surgery in Baseline Season Compared With Influenzalike Illness Season

Characteristics	Baseline Season (n = 13,440)	ILI Season (n = 12,994)	*P* Value
Age, y	68 (61-74)	68 (60-74)	.33
Male	9883 (73.5)	9538 (73.4)	.83
Body mass index, kg/m^2	26.9 (24.3-29.8)	26.8 (24.4-29.8)	.58
Chronic kidney disease	546 (4.1)	540 (4.2)	.73
Malignant neoplasm	40 (0.3)	42 (0.3)	.79
Cirrhosis	40 (0.3)	40 (0.3)	.97
Diabetes mellitus type I or II	2655 (19.8)	2623 (20.2)	.39
NYHA class IV	1015 (7.6)	1068 (8.2)	.05
ACEF II risk score	1.93 (1.36-2.58)	1.98 (1.40-2.65)	.005
APACHE IV predicted mortality	1.21 (0.40-3.06)	1.27 (0.42-3.28)	.003
Academic hospital	5092 (37.9)	5248 (40.4)	<.0001
Intensive care unit occupancy rate	0.98 (0.88-1.10)	1.12 (1.03-1.22)	<.0001

Values are median (interquartile range) or n (%). ACEF II, Age, Creatinine, and Ejection Fraction II; APACHE IV, Acute Physiology and Chronic Health Evaluation IV; ILI, influenzalike illness; NYHA, New York Heart Association.

ILI season. Patients who underwent surgery in the ILI season had a slightly higher APACHE IV predicted mortality, and ICU occupancy rate was higher in ILI season compared with baseline season. Demographics including the intermediate season can be found in Supplemental Table 1.

There were no significant differences between the types of surgery that were performed during baseline season compared with ILI season ($P = .81$; Supplemental Table 2).

In the unadjusted analysis, the P/F ratio was lower in the ILI season 1 day after admission (Table 2). Whereas there was no difference in the ICU length of stay, there was a difference in hospital length of stay, with patients who underwent surgery in the ILI season staying longer. Finally, there was a significant difference in inhospital mortality between groups, with a higher inhospital mortality in the ILI season group. Results including the intermediate group can be found in Supplemental Table 3.

There is a distinct yearly pattern in the number of people with ILI, with differences in the duration of ILI season between the years (Figure 1). Visually, there is no relationship between the ILI prevalence (per 100,000 persons) and the duration of mechanical ventilation in hours.

PRIMARY OUTCOME MEASURE. A Cox regression analysis was performed (Figure 2). For 2015-2016, the hazard ratio (HR) of stopping IMV was 1.22 (95% CI, 1.12-1.33), indicating that independent of other variables, time until IMV interruption was slightly shorter in the ILI season compared with baseline season. Similar results were found for 2014-2015 (HR 1.15; 95% CI, 1.04-1.26) and 2017-2018 (HR 1.25; 95% CI, 1.16-1.36). The HR of stopping IMV did not significantly differ in 2013-2014 (HR 1.14; 95% CI, 0.96-1.34), 2016-2017 (HR 0.99; 95% CI, 0.92-1.07), or 2018-2019 (HR 1.01; 95% CI, 0.93-1.10).

SECONDARY OUTCOME MEASURES. In a multivariable regression analysis, undergoing cardiac surgery during ILI season increased the odds ratio of inhospital mortality (odds ratio 1.67; 95% CI, 1.14-2.46; $P = .009$). The interaction term of ILI season and year of surgery was not significant in a univariable regression analysis and was therefore not included in the multivariable regression analysis, but the individual variables (year of surgery and ILI season) were included.

The season in which cardiac surgery was performed had no significant effect on the P/F ratio on any of the days (Table 3).

The differences in duration of mechanical ventilation between groups for different types of surgery can be seen in Supplemental Table 4. When adding a Bonferroni correction ($\alpha = 0.05$, $m = 12$), setting the significance threshold at 0.0042, there were no differences in hours of mechanical ventilation for a specific type of surgery. The median Age, Creatinine, and Ejection Fraction II risk score and APACHE IV predicted mortality was higher among patients who underwent surgery in an academic hospital compared with patients who underwent surgery in nonacademic hospitals (Supplemental Table 5). A sensitivity analysis excluding the APACHE IV score as a predictor variable in the regression analyses was performed and showed similar results (Supplemental Figure 1, Supplemental Table 6).

TABLE 2 Unadjusted Analysis Showing Differences in Outcomes Between Baseline Season and Influenzalike Illness Season

Variables	Baseline Season (n = 13,440)	ILI Season (n = 12,994)	*P* Value
Duration of mechanical ventilation, h	5.6 (3.5-9.5)	5.6 (3.6-9.5)	.30
P/F ratio 1 day after ICU admission	271 (214-339)	269 (210-332)	.03
P/F ratio 3 days after ICU admission	260 (180-333)	273 (180-348)	.40
P/F ratio 7 days after ICU admission	217 (150-284)	236 (163-304)	.14
Length of stay ICU, d	1.9 (1.1-2.8)	1.9 (1.1-2.9)	.43
Length of stay hospital, d	7.6 (6-11)	8.0 (6-11.1)	<.0001
Inhospital mortality	165 (1.22)	224 (1.72)	.001
ICU mortality	116 (0.86)	125 (0.96)	.43
Ward mortality	49 (0.36)	99 (0.76)	<.0001

Values are median (interquartile range) or n (%). ICU, intensive care unit; ILI, influenzalike illness; P/F, Pa_{O_2} to fraction of inspired oxygen.

COMMENT

In a large Dutch ICU database, we found that patients who underwent elective cardiac surgery in the ILI

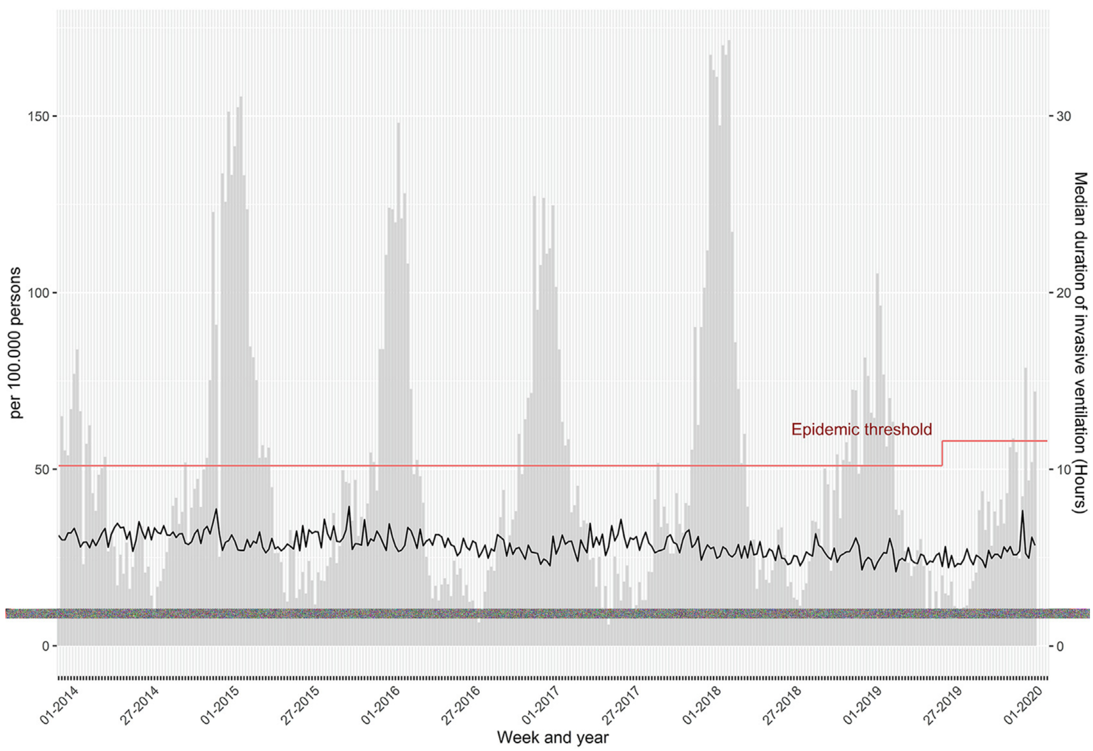

FIGURE 1 Relationship between influenzalike illness prevalence (per 100,000 persons, left Y axis, in light gray) and duration of mechanical ventilation (in hours, right Y axis, black line) between beginning of 2014 and beginning of 2020. Epidemic threshold, which changed in 2019, is drawn in red.

seasons were at increased risk of inhospital mortality compared with patients who underwent cardiac surgery during the baseline seasons. However, we found neither an increase in the duration of mechanical ventilation in hours nor a decrease in the P/F ratio at day 1, 3, or 7 in the ILI seasons compared with baseline seasons.

Earlier research investigating the relationship between viral respiratory disease and outcomes after cardiac surgery also found seasonal differences in outcomes. A study looking at outcomes from more than 16,000 cardiac surgery patients found higher odds of inhospital mortality for patients who underwent surgery in the winter season compared with other seasons.[11] One retrospective study in adults, evaluating a group of patients who underwent cardiac surgery between 2009 and 2011, found a higher prevalence of ARDS and longer duration of IMV in influenza season compared with a season with low prevalence of ILI.[5] Although the ILI season and winter season often overlap, they are not the same. Meteorologic seasonal variety in postoperative complications in noncardiac surgery shows conflicting results, with some studies reporting no seasonal differences,[15] a lower incidence of postoperative infections in winter compared with summer,[16] and higher mortality in winter compared with other seasons.[17]

There are several strengths to this study. First, the large number of patients in the ILI season and baseline season. Second, seven consecutive ILI seasons were included, differing in length, starting time in the year, and severity. We found no clear relationship between the severity of the ILI season and the effect on IMV: 2014-2015 and 2017-2018 were relatively long and severe ILI seasons and 2015-2016 was short and relatively mild; however, in these three seasons, we found a significantly shorter duration of IMV in the ILI season compared with baseline season.[18] Also, all Dutch hospitals that perform cardiac surgery provide data to NICE. Furthermore, as follow-up in our data was continued until hospital discharge, and given the usually early development of pulmonary complications such as ARDS after cardiac surgery,[5] it was possible to compare the occurrence of pulmonary complications through the duration of mechanical ventilation, as it is unlikely severe complications will have occurred after hospital discharge.

There are also some weaknesses that should be considered when interpreting our results. First, using ILI season as a proxy for the risk of respiratory viral infections was a practical solution but also has some downsides. It is an ecologic fallacy to assume that the only difference

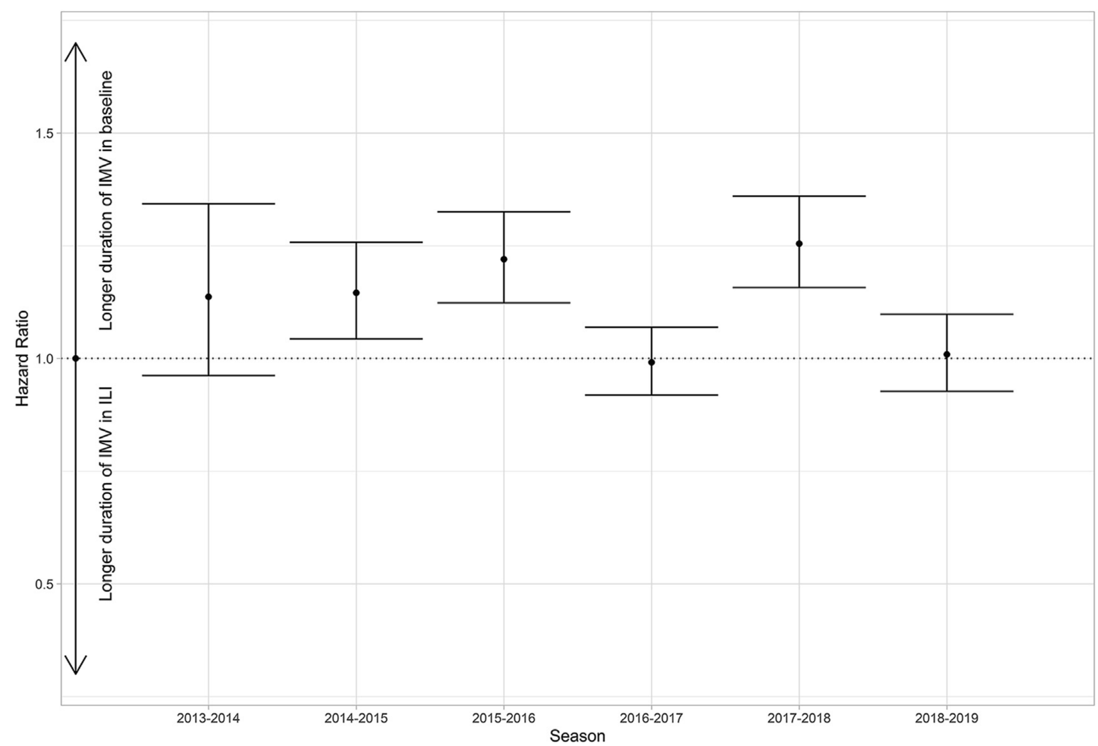

FIGURE 2 Results of Cox regression analysis showing hazard ratio of stopping invasive mechanical ventilation (IMV) in influenzalike illness (ILI) season compared with baseline season for different years. (Influenzalike illness season, year of surgery, age, sex, body mass index, Acute Physiology and Chronic Health Evaluation IV predicted mortality, type of surgery, Charlson comorbidity index, Age, Creatinine, and Ejection Fraction II risk score, hospital type, and intensive care unit occupancy rate were included as predictor variables.)

between ILI season and baseline season is the number of respiratory viral infections. There are environmental differences (average temperature, hours of sunlight), differences in behavior (hours spent outside, exercise), disease frequency (seasonal affective disorder), and differences in some possible risk factors (vitamin D and cholesterol levels).[11,19] Ideally, the possible relationship between asymptomatic respiratory viral infection and pulmonary complications after cardiac surgery should be analyzed using proper viral diagnostics.

Second, there may have been unmeasured confounding, for example, because influenza vaccination status was not available. Because influenza vaccination may also correlate with other factors, such as comorbidity, that could have influenced our results. Likewise, we did not have information on patients who were extubated before ICU admission, although this is very uncommon in the Netherlands. No further information was available on the “other cardiovascular surgery” group, but only a small number of patients were listed in this group. No data on the use of extracorporeal circulation during surgery were available, although the proportion of off-pump procedures is expected to be relatively low and thus have little influence on our results or conclusions.[20]

The gradual increase in inhospital mortality in our study from baseline season through intermediate season to the ILI season is striking and may indicate that current mortality prediction models can be improved. We found no evidence that the difference in inhospital mortality is caused by direct postoperative pulmonary

TABLE 3 Multivariable Linear Regression Analysis

Variables	Estimate (95% CI)	*P* Value
Baseline season	1	
ILI season, P/F day 1	−2.7 (−9.5 to 4.0)	.43
ILI season, P/F day 3	15.8 (−8.2 to 39.8)	.20
ILI season, P/F day 7	−10.2 (−74.8 to 54.4)	.75

Multivariable linear regression analysis with Pa_{O_2} to fraction of inspired oxygen (P/F) ratio on three different days as outcome variables; and age, sex, body mass index, Age, Creatinine, and Ejection Fraction II risk score, type of surgery, Acute Physiology and Chronic Health Evaluation IV predicted mortality, year of surgery, influenzalike illness (ILI) season, Charlson comorbidity index, intensive care unit occupancy rate, and hospital type (academic/nonacademic) as predictor variables.

complications, given the lack of difference in the duration of mechanical ventilation (HR was larger than 1 in all but one ILI season during our study), the absence of a visual relationship between ILI prevalence and duration of IMV or in the P/F ratio in the first week after surgery. Moreover, given that the length of stay in the ICU is the same between seasons, but the length of stay in the hospital is longer in the ILI season, these complications may occur after ICU discharge. Further studies are needed to investigate the cause of this increased inhospital mortality, but possible contributing factors suggested in the literature are the differences in behavior, environmental factors, disease frequency, and risk factors as noted, that could influence the overall condition of patients.

In conclusion, patients undergoing cardiac surgery during ILI season have an increased risk of inhospital mortality compared with patients in the baseline season, but we found no evidence that this difference in mortality is caused by direct postoperative pulmonary complications. Further studies are needed to investigate the cause of the observed increase in inhospital mortality. As we do not have further data, we can only speculate that factors suggested in the literature such as the differences in environmental factors, behavior, disease frequency, and known risk factors that could influence the overall condition of patients could have contributed to changes in mortality risks.

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DISCLOSURES

The authors have no conflicts of interest to disclose.

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