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ORIGINAL ARTICLE

Statins and outcomes of hospitalized patients with laboratory-confirmed 2017–2018 influenza

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Abstract

No studies evaluating the association between statins and outcomes of patients with seasonal influenza have been performed since the 2007–2008 and the 2009 pandemic H1N1 influenza seasons. All consecutive hospitalized patients between October 2017 and April 2018, diagnosed with laboratory-confirmed influenza A and B virus, were included. Patients were divided into two groups: statin and non-statin users. Outcomes were 30- and 90-day mortality, complications (pneumonia, myocarditis, encephalitis, intensive care unit (ICU) transfer, mechanical ventilation, vasopressor support), length of hospital stay, and readmission rates. A multivariate analysis was performed to adjust for mortality risk factors. To compare the groups, we matched patients to the nearest neighbor propensity score. Of the 526 patients ill with influenza A (201/526) and B (325/526), 36% (188/526) were statin users; 64% (338/526) were not. Statin users were older (78 vs.70; $p = < 0.05$) and suffered from more comorbidities (Charlson comorbidity scores of 6 vs.4; $p < 0.005$). The 30-day mortality rate among statin vs. non-statin users was 6% vs. 8% ($p = 0.3$). On multivariate analysis, statin use was not associated with mortality benefit (OR = 0.67 (0.29–1.36)). After propensity score matching, the results were unchanged (OR = 0.71 (0.29–1.71)). Statin users were diagnosed with less complicated diseases as they were less likely to receive vasopressor support, mechanical ventilation, and/or transfer to the ICU. Although statin users were significantly older and exhibited more comorbidities, 30-day mortality rates did not differ between statin users and non-users, which may signify a protective role of statins on seasonal influenza patients. Further studies performed during different influenza seasons and different subtypes are essential.

Keywords Statins · Influenza · Mortality · Outcomes

Introduction

Influenza is associated with increased morbidity and mortality during annual outbreaks with a higher mortality during pandemic years [1–4]. The current therapy for influenza may reduce morbidity and mortality, especially in those who are at risk for complications when suffering from severe illnesses [5–10]. However, the emergence of influenza virus strains resistant to the current antiviral therapy is a constant threat; and in a pandemic situation, the lack of antiviral therapy supplies could exist [11]. The use of statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) has been postulated as an additional tool for the treatment and prophylaxis of influenza due to its cytokine-mediated anti-inflammatory properties, especially in countries where the influenza vaccine and antiviral agents are unavailable [12–17]. Data as to the association of statins on patient outcomes in those hospitalized with influenza are limited.

An observational study [18] demonstrated a decreased mortality with prior statin use (OR = 0.59; 95% CI, 0.4–0.9). Statin users were significantly older and exhibited more comorbidities than the non-users. A retrospective study found a decreased 30-day all-cause mortality with prior statin use during the 2007–2008 season but not during the H1N1 pandemic

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season (HR = 0.41, 95% CI 0.3–0.7; and HR = 0.77, 95% CI 0.4–1.4, respectively) [11]. Another observational study that evaluated immune-modulatory agents, including statins (12 patients) for the treatment of laboratory-confirmed pandemic H1N1 infection, showed no association between statins and disease severity [19]. The aim of our study was to evaluate the association between statins and non-statins on the clinical outcomes of hospitalized patients with laboratory-confirmed influenza infection during the 2017–2018 influenza season. No further data from the 2009 pandemic pH1N1 influenza season has been published.

Methods

We performed a single-center, retrospective analysis of patient data. Electronic records of all consecutive adult patients (≥ 18 years), hospitalized in a 900-bed tertiary, university-affiliated hospital in Israel between October 2017 and April 2018 and diagnosed with laboratory-confirmed influenza A and B virus, were identified and reviewed. Data as to baseline demographics, medications, and chronic comorbidities (including age-adjusted Charlson comorbidity score), as well as malignancy and immunosuppressive condition, were retrieved. Data relating to the index encounter (hospital admission) such as vital signs, laboratory results at presentation, follow-up tests, chest X-ray results, and other data available on admission were collected. Further data included influenza virus serotypes, vaccination status, antiviral drug usage, timing, disease severity, necessity for invasive mechanical ventilation, vasopressor support, and intensive care unit (ICU) admission/transfer during hospitalization. Data were collected from the index point to 90 days post-index episode.

The study cohort was divided into two groups: statin users (study group) and non-users (control group). Patients were included only once in the study. The primary outcome was 30-day all-cause mortality. Secondary outcomes included 90-day all-cause mortality, length of hospital stay (LOS), influenza complications (documented pneumonia, encephalitis or myocarditis, need for mechanical ventilation/vasopressor support/ICU admission/transfer), and rehospitalization rates within 30 days of the index point. The study was approved by the Ethics Committee of the Rabin Medical Center, Petah Tikva, Israel. Informed consent was waived due to the retrospective, non-interventional nature of the study.

Microbiology methods

Influenza detection by the Simplexa™ Flu A/B & RSV test (https://www.focusdx.com/product/ MOL2600) was performed at the Clinical Microbiology Laboratory, Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel. This real-time RT-PCR amplification and detection system utilizes a bi-functional fluorescent probe-primer for the detection and differentiation of human influenza A virus RNA, human influenza B virus RNA, and RSV RNA found on nasopharyngeal swabs. The assay comprises two principal steps: the extraction of RNA from patient specimens; and subsequently, using a bifunctional fluorescent probe-primer together with a reverse primer to amplify a specific target (for each analyte and RNA internal control). Conserved regions of influenza A viruses (matrix gene), influenza B viruses (matrix gene), and the RSV (M gene) were targeted to identify these viruses in the specimen. An RNA internal control was used to monitor the extraction process and detect RT-PCR inhibition.

Statistical analysis

The analysis was performed using the IBM SPSS Statistics, version 22. Statistical significance was set at a two-tailed comparison with $p < 0.05$. To identify individual variables associated with 30-day mortality, a univariate analysis was performed. Normality distribution was assessed through the Kolmogorov–Smirnov normality and Q–Q plot tests. Categorical variables were tested by the Chi-square or Fisher's exact test, as appropriate. Continuous variables were examined by the student's *t* test, if normally distributed or by the Mann–Whitney test, if not. The Hosmer–Lemeshow statistic was used for goodness of fit. A propensity-score model for statin usage was constructed and used to match patients. Variables were entered into the propensity score based on the univariate analysis ($p < 0.1$) or if deemed clinically significant. Matching was performed using the nearest neighbor algorithm (restricted by a caliper equal to 0.02 of the logit of the propensity score) with a 1:2 ratio. In order to identify independent risk factors for mortality, variables significantly associated with mortality in the univariate analysis and not highly correlated were entered into the multivariate logistic regression model. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for 30-/90-day mortality were calculated. Pre-defined subgroup analysis included patients with influenza A/B, vaccination status, antiviral treatment, and state of the immune deficiency (defined as organ transplant, active therapy for malignancy, high-dose steroids/other iatrogenic drugs, and conditions).

Results

Study cohort at presentation

During the 2017–2018 influenza season, a total of 526 consecutive patients were hospitalized with laboratory-confirmed influenza A (201/526) and B (325/526). Baseline and admission data of the patients are presented in Table 1. The median age of the entire cohort was 74 (62–83) years; the majority of patients resided in long-term care facilities (LTCF) (74%).

Table 1 Baseline characteristics of hospitalized patients with laboratory-confirmed influenza divided into two groups: statin users and non-statin users

Variables	Entire cohort ($n = 526$)	Statin users ($n = 188$)	Non-statin users ($n = 338$)	p value
Age (median 25–75%)	74 (62–83)	78 (71–84)	70 (55.75–83)	0.0001
Female gender, *n* (%)	268 (51%)	85 (45%)	183 (54%)	0.05
BMI (median 25–75%)	26 (23–30)	27.3 (24–31)	25 (26–29)	0.003
Assisted in ADL, *n* (%)	126/514 (25%)	44/182 (24%)	82/332 (25%)	0.9
Home residency, *n* (%)	133/513 (26%)	58/182 (32%)	75/331 (23%)	0.02
Age-adjusted Charlson score (median 25–75%)	5 (3–7)	6 (4–8)	4 (2–6)	0.0001
Admission diagnosis				
Flu-like symptoms, *n* (%)	310/490 (63%)	112/181 (62%)	198/309 (64%)	0.3
Other infections, *n* (%)	89/490 (18%)	29/181 (16%)	60/309 (19%)	
Non-infectious disease, *n* (%)	91/490 (19%)	40 /181 (22%)	51/309 (17%)	
Comorbidities				
Active smoking, *n* (%)	43 (8%)	17 (9%)	26 (8%)	0.6
Dementia, *n* (%)	28 (5%)	7 (4%)	21 (6%)	0.2
Hypertension, *n* (%)	239 (45%)	121 (64%)	118 (35%)	0.0001
Ischemic heart disease, *n* (%)	100 (19%)	57 (30%)	43 (13%)	0.0001
Congestive heart failure, *n* (%)	61 (12%)	27 (14%)	34 (10%)	0.1
Chronic obstructive lung disease, *n* (%)	56 (11%)	23 (12%)	33 (10%)	0.4
Peripheral vascular disease, *n* (%)	22 (4%)	10 (5%)	12 (4%)	0.3
Cerebrovascular accident, *n* (%)	59 (11%)	36 (19%)	23 (7%)	0.0001
Chronic kidney disease, *n* (%)	43 (8%)	16 (9%)	27 (8%)	0.8
Hyperthyroidism, *n* (%)	7 (1%)	2 (1%)	5 (2%)	1
Hypothyroidism, *n* (%)	33 (6%)	13 (6%)	20 (6%)	0.7
Liver disease, *n* (%)	6 (1%)	0 (0%)	6 (2%)	0.09
Diabetes mellitus, *n* (%)	168 (32%)	88 (47%)	80 (24%)	0.0001
Malignancy, *n* (%)	46 (9%)	18 (10%)	28 (8%)	0.6
Organ transplant, *n* (%)	23 (4%)	8 (4%)	15 (4%)	0.9
Vital signs				
Temperature, in Celsius (median 25–75%)	37.5 (36.9–38.3)	37.5 (37–38.4)	37.4 (36.8–38.2)	0.1
Systolic blood pressure (mmHg, median 25–75%)	119 (107–135)	124 (108.2–140.7)	117 (105–132)	0.0001
Saturation (median 25–75%)	95 (92–97)	94 (91–96)	96 (93–98)	0.001
Pulse (median 25–75%)	96 (85–109)	94 (85–107)	97 (85–110)	0.5
Medication history				
Systemic steroid, *n* (%)	102 (19%)	36 (19%)	66 (20%)	0.9
Iron supplements, *n* (%)	29 (6%)	12 (6%)	17 (5%)	0.5
Immunosuppressive, *n* (%)	32 (6%)	11 (6%)	21 (6%)	0.9
Bisoprolol, *n* (%)	134 (26%)	61 (32%)	73 (22%)	0.006
Metformin, *n* (%)	79 (15%)	50 (27%)	29 (9%)	0.0001
Infection characteristics and management				
Influenza A virus, *n* (%)	201 (38%)	74 (39%)	127 (38%)	0.7
Influenza B virus, *n* (%)	325 (62%)	114 (61%)	211 (62%)	0.7
Tamiflu therapy, *n* (%)	357 (68%)	128 (68%)	229 (68%)	0.9
Directed Tamiflu therapy, *n* (%)	148/352 (42%)	46/127 (36%)	102/225 (45%)	0.09
Flu vaccination, *n* (%)	87 (17%)	42 (22%)	45 (13%)	0.008
Infection severity and complications				
Myocarditis, *n* (%)	2 (0.4%)	0 (0%)	2 (0.6%)	0.5
Encephalitis, *n* (%)	2 (0.4%)	0(0%)	2 (0.6%)	0.5
ICU transfer, *n* (%)	20 (4%)	4 (2%)	16 (5%)	0.1
Mechanical ventilation, *n* (%)	19 (4%)	3 (2%)	16 (5%)	0.07
Vasopressors, *n* (%)	17 (3%)	3 (2%)	14 (4%)	0.1
X-ray				
Normal, *n* (%)	206/299 (69%)	81/111 (73%)	125/188 (67%)	0.007
Consolidation, *n* (%)	29/299 (10%)	3/111 (3%)	26/188 (14%)	0.007
Other, *n* (%)	64/299 (21%)	27/111 (24%)	37/188 (20%)	0.007
Outcomes				
Readmission 90 days, *n* (%)	126 (24%)	48 (26%)	78 (23%)	0.5
30-Day mortality, *n* (%)	39 (7%)	11 (6%)	28 (8%)	0.3
90-Day mortality, *n* (%)	57 (11%)	18 (10%)	39 (12%)	0.5
Length of hospital stay (median 25–75%)	4 (2–6)	4 (2–6)	3 (2–7)	0.9

More than half (63%) were hospitalized at admission, and diagnosed with flu-like symptoms (310/410). Only 17% had been inoculated with the annual influenza vaccine. Of the 526 hospitalized patients, 36% (188/526) were statin users, whereas 64% (338/526) were not. Statin users were significantly older (median age 78 vs.70, $p \leq 0.05$), and were more likely to reside in LTCF compared with the non-users (32% vs. 23%, $p \leq 0.05$). Furthermore, statin users had higher age-

adjusted Charlson scores (median 6 vs. 4; $p \leq 0.005$) and were more likely to have significant cardiovascular comorbidities, such as ischemic heart disease and cerebrovascular diseases. Patients receiving active therapy for a malignancy, organ transplants, and other immunosuppressive conditions were similarly distributed between the two groups. Statin users were significantly more likely to receive their annual influenza vaccine than the non-users (22% vs. 13%; $p = 0.008$) (Table 1). At presentation, vital signs on admission were similar between the two groups except for oxygen saturation at room air, which was slightly lower in the statin group (median room-air oxygen saturation was 94% (91–96%) vs. 96% (93–98%). Over half of the patients in both groups were infected with the influenza B virus (61% vs. 62%); 68% had received empirical antiviral therapy on admission (Table 1).

Primary outcome: 30-day all-cause mortality

The crude 30-day mortality rate for the entire cohort was 8% (39/526). The 30-day all-cause mortality rates in the statin group were less than the non-statin, 6% vs. 8%, respectively (p = NS). A univariate analysis followed by a multivariate analysis identified the risk factors for 30-day mortality (Table 2). Univariate analysis demonstrated that mortality at 30 days was associated with increased age, chronic comorbidities, assisted living, and certain laboratory results (higher CRP and creatinine and troponin levels, and lower albumin levels). Patients who died before 30 days presented on admission with vital signs similar to patients who had survived after 30 days, except for lower systolic blood pressure for non-survivors (median 112 vs. 120 mmHg), additional vasopressor support, mechanical ventilation, and ICU transfer. Mortality was found associated with not receiving antiviral therapy (43% vs. 59%), and a longer time to initiation of the therapy (31.5 vs. 20 h). Mortality did not increase with statin non-usage (36% vs. 28%, $p = 0.3$). Multivariate analysis demonstrated that increased age, reduced admission albumin levels, increased age-adjusted Charlson score, and the need for vasopressor support were associated with mortality at 30 days. After adjustment for other risk factors of mortality, statin use showed no association with mortality (OR = 0.67; CI 95% [0.29–1.36]) (Table 3). After 1:2 propensity score matching, we repeated the above analysis (Table 3). The results for the 30-day mortality on multivariate analysis were unchanged between the matched and unmatched populations.

Secondary outcomes: 90-day all-cause mortality, complication, LOS, readmission

The crude mortality rate at 90 days for the entire cohort was 11% (57/526). Mortality rates between statin users and non-users did not significantly vary (10% vs. 12%, $p = 0.5$). During hospitalization, the statin non-users exhibited a more complicated disease as they were more likely to receive vasopressor support, mechanical ventilation, and ICU transfer (Table 1). Lower respiratory infections observed on chest X-rays performed on admission or during hospitalization were observed less in statin users (3% vs. 14%, $p = 0.007$). There have been no documented cases of myocarditis or encephalitis in statin users compared with two cases of each in the control group (0 vs. 2, 0 vs. 2; $p = 0.5$, respectively). A non-significant increase in LOS of 1 hospital day (median 3 vs. 4 days; $p = 0.9$) was observed in statin users. Readmission rates at 30 days from the index point were similar for statin and non-statin users (26% vs. 23%, $p = 0.5$).

Discussion

This is the first study to evaluate the association of statin usage on disease severity, complications, and mortality of seasonal influenza since the 2009 pandemic H1N1 season. The current study demonstrated that during the 2017–2018 influenza season, mortality rates at 30 days did not statistically differ between statin and non-statin users, although the former were significantly older and exhibited more baseline comorbidities and a positive net estimate of statins on mortality. In addition, statin users suffered from a less complicated disease which may signify a protective role of statins on seasonal influenza patients.

In our study, despite the statistically non-significant association of statins on mortality, the effect estimate of morality was reduced in statin users (OR 0.67), as demonstrated in previous studies [11, 18] of laboratory-confirmed influenza. Furthermore, statin users exhibited a less complicated disease course (less pneumonia, no documented cases of myocarditis or encephalitis, and were less likely to receive cardiovascular support, mechanical ventilation, and ICU transfer), thus strengthening our assumption that there are positive immunomodulation properties of statins in those suffering from influenza. Statin users in our cohort were older and had significant chronic cardiovascular and respiratory conditions, thus putting them at risk for adverse outcomes and hospitalization. A possible explanation of this observation was the beneficial anti-inflammatory and immunomodulatory pleiotropic effects of statins that we and others have shown in other infectious diseases including pneumonia, *Clostridium difficile* infection, and bacteremia [20–22]. Statins reduce the release of cytokines and acute-phase reactants, alter the cellular chemotaxis of the immune system, inhibit the synthesis of products of mevalonate pathway, such as isoprenoids and geranylgeranylpyrophosphate, and have antioxidant properties [23, 24]. Another explanation is the "healthy user effect." Statin users tend to live at home, adhere to chronic medications, and engage in other positive health behaviors including adherence to an annual influenza vaccination schedule. Whether the

Table 2 Univariate analysis of statins and other risk factors for 30-day mortality

Variable	Dead ($n = 39$)	Survived ($n = 487$)	p value
Age (median 25–75%)	84 (74–89)	73 (62–82)	0.0001
Female gender, *n* (%)	22 (56%)	245 (51%)	0.5
Assisted ADL, *n* (%)	19/38 (50%)	107/476 (22.5%)	0.0001
Age-adjusted Charlson score (median 25–75%)	6 (5–7)	5 (3–7)	0.004
Home residency	10/38 (26%)	123/475 (26%)	0.9
Admission diagnosis			
Flu-like symptoms, *n* (%)	21/39 (54%)	289/451 (64%)	0.4
Other infections, *n* (%)	8/39 (21%)	81/451 (18%)	
Non-infectious disease, *n* (%)	10/39 (26%)	81/451 (18%)	
Comorbidities			
Organ transplant, *n* (%)	2 (5%)	21 (4%)	0.7
Malignancy, *n* (%)	1 (3%)	45 (9%)	0.2
Congestive heart failure, *n* (%)	8 (21%)	53 (11%)	0.07
Chronic kidney disease, *n* (%)	7 (18%)	36 (7%)	0.02
Diabetes mellitus, *n* (%)	11 (28%)	157 (32%)	0.7
Infection characteristics and management			
Influenza A virus serotype, *n* (%)	16 (41%)	185 (38%)	0.7
Influenza B virus serotype, *n* (%)	23 (59%)	302 (62%)	0.7
Tamiflu therapy, *n* (%)	28 (72%)	329 (68%)	0.6
Directed Tamiflu therapy, *n* (%)	16/28 (57%)	132/324 (41%)	0.09
Flu vaccination, *n* (%)	3 (8%)	84 (17%)	0.2
Symptom ER duration (median 25–75%)	2 (1–4)	3 (1–5)	0.1
Symptom treatment duration (median 25–75%)	3.5 (2–5)	3 (2–5)	0.7
Time to treatment start (median hours)	31.5 (14.5–2.25)	20 (12–35)	0.02
Disease severity and complications			
Vasopressor use, *n* (%)	7/38 (18%)	10/482 (2%)	0.0001
Mechanical ventilation, *n* (%)	11 (28%)	8 (2%)	0.0001
ICU transfer, *n* (%)	5 (13%)	15 (3%)	0.002
Myocarditis, *n* (%)	0 (0%)	2 (0.4%)	1
Encephalitis, *n* (%)	0 (0%)	2 (0.4%)	1
X-ray, *n* (%)			
Normal, *n* (%)	8/23 (35%)	198/276 (72%)	0.001
Consolidation, *n* (%)	4/23 (17%)	25/276 (9%)	
Other, *n* (%)	11/23 (48%)	53/276 (83%)	
Vital signs at presentation			
Temperature (median 25–75%)	37.4 (36.9–37.8)	37.5 (36.9–38.3)	0.5
Systolic blood pressure (mmHg) (median 25–75%)	112 (100–119)	120 (108–136)	0.004
Oxygen saturation (median 25–75%)	93 (88–98)	95 (92–97)	0.8
Pulse rate (beats per minute) (median 25–75%)	92 (81–120)	96 (86–109)	0.8
Lab results at presentation			
Glucose level (mg/dl), *n* (%)	159 (127–221)	136 (108–177)	0.04
Hemoglobin level (mg/dl), *n* (%)	9.9 (8–12)	11 (10–13)	0.05
Troponin level (mg/dl), *n* (%)	184 (72–442)	43 (26–78)	0.005
Creatinine level (mg/dl), *n* (%)	1.76 (1.1–2.8)	1.06 (0.8–1.4)	0.0001
Albumin level (mg/dl), *n* (%)	3.1 (2.6–3.55)	3.6 (3.2–4)	0.000
WBC level (mg/dl), *n* (%)	9.8 (6.2–12.5)	8.2 (6–11)	0.2
CRP level (mg/dl), *n* (%)	8.74 (3.5–22)	5.33 (2.5–12)	0.06
Medication history			
Prior statin use	11 (28%)	177 (36%)	0.3
Bisoprolol use	15 (39%)	119 (24%)	0.053
Immunosuppressive therapy	3 (8%)	29 (6%)	0.7
Systemic steroid therapy	10 (26%)	92 (19%)	0.3

higher rates of influenza vaccination in statin users have attributed to less severe and complicated disease course is still unclear.

Another important observation was the predominance of the influenza B virus that was disseminated during the 2017–2018 season, whereas in previous studies [11, 18], influenza A was the predominant virus (H3N2 during the 2007–2008 season). It appears that there was a difference in statin efficacy as opposed to the emerging influenza virus strain. Statin usage was protective in seasons where the influenza A H3N2 virus was the main circulating one; however, the protective role was lost in seasons where the influenza A subtype H1N1 was predominant. Whether a variation in the degree of cytokine dysregulation is caused by different influenza virus types and subtypes is vague and should be further investigated.

Table 3 Multivariate logistic regression model for risk factors for 30-day mortality (Hosmer–Lemeshow goodness of fit test $p = 0.053$, $\beta = -0.411$, $N = 494$)

Variable	Univariate OR (95% CI)	Multivariate OR (95% CI)	Adjusted propensity score ($N = 491$)	p value
Age-adjusted Charlson score	1.68 (1–1.3)	1.19 (1.04–1.4)	1.18 (1.01–1.37)	0.01
ICU transfer	4.62 (1.6–13.5)	1.35 (0.4–1.6)	1.002 (0.23–4.26)	0.7
Albumin level (mg/dl) at presentation	0.27 (0.2–0.5)	0.4 (0.2–0.7)	0.31 (0.16–0.57)	0.001
Creatinine level (mg/dl) at presentation	1.37 (1.2–1.6)	1.21 (0.9–1.5)	1.19 (0.96–1.48)	0.09
Vasopressor administration	10.7 (3.8–30)	7.01 (2.1–24)	5.47 (1.53–19.52)	0.002
Statin use	0.68 (0.3–1.4)	0.67 (0.3–1.4)	0.71 (0.29–1.71)	0.4

A few published studies relating to the association between statin usage and outcomes including mortality have been found in the literature, all conducted during the influenza seasons prior to the 2009 pandemic H1N1 season. In a population-based study, covering 10 influenza seasons (1996–2006), which included elderly Canadian patients, statins exhibited a protective role on mortality (OR = 0.87; 95% CI 0.84–0.89) [25]. During the same time period, Frost et al. [26] conducted a matched cohort study evaluating the association between statin usage and mortality from influenza using data from a health maintenance organization in New Mexico from 1992 through 2003. They found a statistically significant reduced OR of influenza and death from pneumonia (OR = 0.17; 95% CI 0.07–0.42) [26]. In these two studies, however, the diagnosis of influenza was not laboratory confirmed and relied mainly on data documented in the patients' medical records. Moreover, in the later study, the diagnosis of influenza was based on combined ICD-9 codes (influenza and pneumonia) that might have led to misclassification of disease outcomes.

A large observational multi-center, multi-state study was conducted by Vandermeer et al. [18] on hospitalized patients with laboratory-confirmed influenza during the 2007–2008 season. One-third (1013/3043) of the patients received prior or concomitant statin therapy. Statin users were older and exhibited more baseline comorbidities compared with the control group. In the multivariate analysis, statins were found associated with decreased mortality (OR = 0.59; 95% CI 0.4–0.9) [18]. The statin users in our study compared with the statin users in Vandermeer et al.'s study were older, had resided longer in LTCF, had fewer documented influenza vaccinations, and had received less antiviral therapy during their hospital stay. A Spanish study evaluated the treatment of 197 hospitalized patients with laboratory-confirmed H1N1 influenza with different immune-modulatory agents including statins (12 patients) and found no significant association between statins and disease severity (OR = 0.64; 95% CI 0.22–1.86) [19]. Another study used population-based influenza surveillance data to assess the association between statin usage and mortality among hospitalized cohorts during two influenza seasons (2007–2008 and 2009 pandemic). The propensity score matched analysis revealed that statin usage was protective against death from influenza at 30 days in the 2007–2008 cohort (HR 0.41; 95% CI 0.25–0.68); however, this association was not significant in the 2009 pandemic pH1N1 influenza cohort (HR 0.77; 95% CI 0.43–1.36) [11].

Our study has several limitations. Firstly, since this is a retrospective study, data on influenza vaccination were difficult to retrieve, with only a small number of patients disclosing a documented influenza vaccine. We, therefore, could not include influenza vaccine status in the multivariate analysis for mortality which might have substantially affected the results. Moreover, it is more likely that the vaccination rate was higher among elderly patients (statin users) who suffer from a higher risk of influenza complications than younger patients (statin non-users). Secondly, although the statin users were older and sicker than the non-statin users, the latter group included patients ($n = 14$) who required vasopressor therapy (vs. 3 among the statin users). This difference was not statistically significant (2% vs. 4%); however, vasopressor treatment exhibited the strongest association with mortality (OR = 7) which might imply that among the non-statin users, there was a group of patients who were severely ill. This could lead to higher mortality rates than expected and not the protective role of statins that led to the lower mortality rates in the statin group. Thirdly, the study was based on a cohort from a single institution and should be validated by additional prospective research involving other populations during the same season. Lastly, influenza A virus subtypes (H1N1 or H2N3) were not detected by the neighbor test method used during this study.

Conclusion

During the 2017–2018 influenza season, predominated by the influenza B virus, statin treatment was associated with less complications and 30-day mortality rates from influenza. As this protective association was demonstrated only during the 2007–2008 influenza season, predominately by the H3N2 subtype, further studies researching different influenza seasons are essential.

Contributors All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Alaa Atamna, Tanya Babich, and Mayaan Bracha. The first draft of the manuscript was written by Alaa Atamna and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Ethics Committee of the Rabin Medical Center, Petah Tikva, Israel, RMC-18-0297) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was waived because of the retrospective, non-interventional nature of the study.

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