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The association between COVID-19 infection and incident atrial fibrillation: results from a retrospective cohort study using a large US commercial insurance database

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ABSTRACT

Background We sought to examine a 1-year incidence of atrial fibrillation (AF) among patients with SARS-CoV-2 virus (COVID-19) in comparison to those with non-COVID-19 acute upper respiratory infection (AURI).

Methods Patients with a diagnosis of COVID-19 (in any setting) between April 2020 and June 2021 were identified in Optum Clinformatics. Two comparator cohorts were constructed: an 'AURI pandemic' cohort (AURI diagnosis between April 2020 and June 2021) and an 'AURI prepandemic' cohort (AURI diagnosis between January 2018 and December 2018). One-year incidence of AF was compared among: COVID-19 versus AURI pandemic cohort; COVID-19 versus AURI prepandemic cohort; and AURI pandemic versus AURI prepandemic cohort. For each comparison, we applied a matching weights technique to balance covariates. Logistic regression was used to compare the odds of incident AF among the matched cohorts.

Results When comparing the matched COVID-19 (n=102 227) cohort with the AURI pandemic (n=102 101) cohort, higher incidence of AF was observed among the COVID-19 cohort (2.2% vs 1.2%; p<0.001; OR 1.83; 95% CI 1.72 to 1.95). Similar findings were observed for the COVID-19 (n=169 687) versus AURI prepandemic (n=169 486) comparison (2.7% vs 1.6%; p<0.001; OR 1.70; 95% CI 1.63 to 1.78). When comparing the AURI pandemic (n=1 26 392) versus AURI prepandemic (n=1 26 394) cohort, no significant differences in incident AF were observed (1.1% vs 1.2%; p=0.133; OR 0.95, 95% CI 0.90 to 1.01).

Conclusion Patients diagnosed with COVID-19 were found to be at a higher risk of incident AF as compared with those with AURI. Timely diagnosis and appropriate treatment of AF may potentially mitigate the burden of AF conferred by COVID-19.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ A few studies have found an association between COVID-19 and cardiovascular-related morbidities, including cardiac arrhythmias among hospitalised patients with COVID-19.

WHAT THIS STUDY ADDS

⇒ Our study is among the first to assess the relationship between COVID-19 and atrial fibrillation (AF) among patients treated for COVID-19 in acute care (eg, in-patient hospital) and non-acute care settings (eg, community-based primary care office), with the risk of AF observed to be elevated among patients with COVID-19 in comparison to non-COVID-19 acute upper respiratory infections.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Increased risk of AF seems to be unique to infection with COVID-19. Healthcare providers may consider routine screening for AF among patients with prior history of COVID-19 to aid in timely diagnosis and treatment of AF.

INTRODUCTION

Since its emergence in 2019, SARS-CoV-2 (COVID-19) has led to considerable morbidity and mortality globally.[1–5] A few studies have examined the relationship between COVID-19 and new-onset atrial fibrillation (AF), with mixed results.[6–13] AF is a common arrhythmia conferring its own risks of complications, many of which align with those associated with COVID-19 (eg, stroke, heart failure and death).[6–13] In their study comparing the incidence of AF among patients hospitalised with COVID-19 versus those hospitalised without COVID-19, Wollborn *et al* observed the COVID-19 cohort to have 19% higher risk of new onset AF (OR 1.19; 95% CI 1.00 to 1.41) as compared with the non-COVID-19 cohort.[14] In contrast, when comparing outcomes among patients hospitalised with COVID-19 to those hospitalised with influenza in France, Piroth *et al* observed a significantly lower risk of

Figure 1 Attrition steps. AAD, antiarrhythmic drug; AF, atrial fibrillation; AURI, acute upper respiratory infection.

developing AF (12.4% vs 15.8%; p<0.0001) among the former cohort as compared with the latter.[15]

While these prior studies offer critical insights, the apparent inconsistencies in their findings make it difficult to draw further conclusions on the potential causal relationship between COVID-19 and AF. Further, these studies have focused on patients hospitalised with COVID-19, representing a sicker cohort of patients affected by COVID-19. Though rates of COVID-19 hospitalisation have been substantial and varied by different phases of the pandemic, it may be argued that a considerably higher proportion of COVID-19 cases were treated in a community setting. The objective of this study was to assess the 12-month risk of incident AF among patients diagnosed with COVID-19 when compared with those with non-COVID-19 acute upper respiratory infections (AURI) in a broad population of patients treated in non-acute and acute care settings.

METHODS

Data source

The Optum Clinformatics database, which is a nationally representative administrative claims database of commercially insured (including Medicare Advantage) patients in the USA, was used for study purposes.[16 17] The database includes medical services, prescription fill, demographic and enrolment information for UnitedHealth commercial insurance plan members.[16 17]

Study population

For the COVID-19 cohort, we included patients 21 years of age or above who had one or more medical service visits with a primary diagnosis of COVID-19 (International Classification of Disease, Tenth Revision, Clinical Modification (ICD-10-CM) code U07.1; in any setting) between April 2020 and June 2021. Two comparator cohorts (pandemic and pre pandemic) involving patients 21 years of age or greater with at least one medical service visit with a primary diagnosis of AURI (pandemic (between April 2020 and June 2021) or pre pandemic (between January 2018 and December 2018)) were also created. An AURI diagnosis was defined as any of the following ICD-10-CM codes: J00, J01, J010, J0100, J0101, J011, J0110, J0111, J012, J0120, J0121, J013, J0130, J0131, J014, J0140, J0141, J018, J0180, J0181, J019, J0190, J0191, J02, J020, J028, J029, J03, J030, J0300, J0301, J038, J0380, J0381, J039, J0390, J0391, J04, J040, J041, J0410, J0411, J042, J043, J0430, J0431, J05, J050, J051, J0510, J0511, J06, J060, J069. The initial COVID-19 (for the COVID-19 cohort) or AURI diagnosis (for AURI pandemic/prepandemic cohorts) date was considered as the index date. Consistent across all cohorts, patients were excluded if there was a record of them having any of the following in the pre index period: COVID-19, AURI, prior AF diagnosis, an antiarrhythmic prescription drug claim or a catheter ablation procedure. For all three cohorts, continuous enrolment was required throughout the 12-month pre index and post index period. For the AURI pandemic cohort, an additional exclusion criterion was record of a COVID-19 diagnosis in the entire study period.

Study variables

The primary outcome of interest was incident AF diagnosis (ICD-10-CM I480, I481, I4811, I4819, I482, I4820, I4821, I4891; in any setting) in the 365 days post index period. Study covariates included: age (21–49, 50–69, 70 and above years of age), sex at birth (male, female), race/ethnic affiliation (white, black, Asian, Hispanic, other), geographic region (Northeast, Midwest, South, West), annual household income (<US$50k, US$50k–US$99k, ≥US$100k), education (<bachelor's degree, ≥bachelor's degree), Elixhauser Comorbidity Score (0.1–3.4+), CHA_2DS_2–VASc Score (0.1–3.4+), congestive heart failure, valvular disease, obesity, diabetes (uncomplicated and complicated diabetes), hypertension (uncomplicated and complicated hypertension), pulmonary circular disorders, peripheral vascular disease, prior history of cardiac surgery, obstructive sleep apnoea, hyperthyroidism, alcohol-related disorders, congenital heart disease and time of index diagnosis (per annual quarter; only considered for the COVID-19 cohort vs AURI pandemic cohort comparison).

Statistical analysis

Comparison of incident AF outcome was made across the three study cohorts: COVID-19 cohort versus AURI pandemic cohort; COVID-19 cohort versus AURI prepandemic cohort; and AURI pandemic cohort versus AURI prepandemic cohort. For each comparison, a matching weight method (developed by Yoshida *et al*)[18] was used to achieve covariate balance between cohorts. Covariate balance was determined using standardised mean differences (SMDs) with value above 0.1 or less than −0.1 indicative of imbalance.[19] SMDs are commonly used as an assessment metric to compare the mean of covariates (dichotomous, categorical and continuous) between arms or groups.[18 20] As compared with other assessment metrics, SMDs are advantageous for a few reasons including that SMDs are not impacted or influenced by study population size.[20] Consistent with Yoshida *et al* approach,[18] we used the table one package to calculate all SMDs (pre weight and post weight covariate balance assessment).[18 21] For each comparison, a weighted logistic regression model was then built to compare the odds of incident AF between cohorts. Any covariates that were not balanced based on SMD criteria post matching were adjusted in the regression model.[22]

Next, we performed subanalysis by sex and age categories, as well as by hypertension status. For subanalysis, samples subset by sex (male, female), by age (21–49 years,

Table 1 Sample characteristics of patients with COVID-19 and patients with acute upper respiratory infection (pandemic)

	Pre match			Post match		
	COVID-19	AURI (pandemic)		COVID-19	AURI (pandemic)	
	n=174 432	n=126 392	SMD	n=102 227	n=102 101	SMD
Age (categorical)			0.246			0.002
21–49	57 879 (33.2%)	54 589 (43.2%)		41 267 (40.4%)	41 213 (40.4%)	
50–69	61 618 (35.3%)	43 901 (34.7%)		36 188 (35.4%)	36 072 (35.3%)	
70 and above	54 935 (31.5%)	27 902 (22.1%)		24 772 (24.2%)	24 816 (24.3%)	
Gender—male	89 596 (51.4%)	54 182 (42.9%)	0.171	46 589 (45.6%)	46 681 (45.7%)	0.003
Geographic region			0.157			0.01
Northeast	25 453 (14.6%)	12 281 (9.7%)		11 503 (11.3%)	11 299 (11.1%)	
Midwest	45 358 (26.0%)	35 491 (28.1%)		27 973 (27.4%)	28 216 (27.6%)	
South	73 042 (41.9%)	53 285 (42.2%)		42 871 (42.0%)	42 871 (42.0%)	
West	30 579 (17.5%)	25 335 (20.0%)		19 715 (19.3%)	19 715 (19.3%)	
Race			0.215			0.003
Asian	6451 (3.7%)	4152 (3.3%)		3551 (3.5%)	3540 (3.5%)	
Black	20 906 (12.0%)	12 274 (9.7%)		10 764 (10.5%)	10 720 (10.5%)	
Hispanic	31 573 (18.1%)	14 703 (11.6%)		13 778 (13.5%)	13 656 (13.4%)	
Unknown	3427 (2.0%)	2408 (1.9%)		1972 (1.9%)	1977 (1.9%)	
White	112 075 (64.3%)	92 855 (73.5%)		72 163 (70.6%)	72 209 (70.7%)	
Education≥bachelor's degree	29 916 (17.2%)	24 755 (19.6%)	0.063	19 382 (19.0%)	19 318 (18.9%)	0.001
Annual household income			0.1			0.002
<US$50k	61 028 (35.0%)	39 506 (31.3%)		32 964 (32.2%)	32 951 (32.3%)	
US$50k–US$99k	52 116 (29.9%)	43 140 (34.1%)		35 518 (34.7%)	35 542 (34.8%)	
≥US$100k	61 288 (35.1%)	43 746 (34.6%)		33 746 (33.0%)	33 609 (32.9%)	
Elixhauser Score category			0.183			0.001
0	59 943 (34.4%)	49 779 (39.4%)		39 252 (38.4%)	39 274 (38.5%)	
1–3	75 513 (43.3%)	57 160 (45.2%)		45 600 (44.6%)	45 500 (44.6%)	
4+	38 976 (22.3%)	19 453 (15.4%)		17 375 (17.0%)	17 327 (17.0%)	
CHA_2DS_2–VASc Score			0.22			0.002
0	39 245 (22.5%)	28 781 (22.8%)		23 815 (23.3%)	23 865 (23.4%)	
1–3	94 873 (54.4%)	78 915 (62.4%)		61 879 (60.5%)	61 745 (60.5%)	
4+	40 314 (23.1%)	18 696 (14.8%)		16 533 (16.2%)	16 492 (16.2%)	
Congestive heart failure—yes	9212 (5.3%)	3371 (2.7%)	0.134	3244 (3.2%)	3235 (3.2%)	<0.001
Valvular disease—yes	8929 (5.1%)	4771 (3.8%)	0.065	4181 (4.1%)	4174 (4.1%)	<0.001
Obesity—yes	27 850 (16.0%)	17 222 (13.6%)	0.066	14 533 (14.2%)	14 489 (14.2%)	0.001
Diabetes—yes	38 788 (22.2%)	17 878 (14.1%)	0.211	16 333 (16.0%)	16 355 (16.0%)	0.001
Hypertension—yes	78 471 (45.0%)	44 917 (35.5%)	0.194	38 777 (37.9%)	38 689 (37.9%)	0.001
Pulmonary circulation disorders—yes	2944 (1.7%)	1351 (1.1%)	0.053	1245 (1.2%)	1242 (1.2%)	<0.001
Peripheral vascular disease—yes	18 394 (10.5%)	7829 (6.2%)	0.158	7303 (7.1%)	7269 (7.1%)	0.001
Obstructive sleep apnoea—yes	14 344 (8.2%)	9466 (7.5%)	0.027	7893 (7.7%)	7869 (7.7%)	0.001
Hyperthyroidism—yes	977 (0.6%)	608 (0.5%)	0.011	505 (0.5%)	511 (0.5%)	0.001
Prior history of cardiac surgery—yes	2591 (1.5%)	1241 (1.0%)	0.046	1113 (1.1%)	1113 (1.1%)	<0.001
Alcohol-related disorders—yes	2523 (1.4%)	1862 (1.5%)	0.002	1495 (1.5%)	1480 (1.4%)	0.001
Congenital heart disease—yes	888 (0.5%)	580 (0.5%)	0.007	473 (0.5%)	473 (0.5%)	<0.001
Per annual quarter (index date)*			0.55			0.007
Q2 2020	16 836 (9.7%)	21 268 (16.8%)		14 366 (14.1%)	14 258 (14.0%)	
Q3 2020	25 701 (14.7%)	22 364 (17.7%)		19 256 (18.8%)	19 295 (18.9%)	

Continued

Table 1 Continued

	Pre match			Post match		
	COVID-19	AURI (pandemic)		COVID-19	AURI (pandemic)	
	n=174 432	n=126 392	SMD	n=102 227	n=102 101	SMD
Q4 2020	68 484 (39.3%)	31 156 (24.7%)		31 330 (30.6%)	31 120 (30.5%)	
Q1 2021	48 978 (28.1%)	23 268 (18.4%)		23 236 (22.7%)	23 170 (22.7%)	
Q2 2021	14 433 (8.3%)	28 336 (22.4%)		14 040 (13.7%)	14 258 (14.0%)	

*Index date is date of initial COVID-19 or AURI diagnosis (during pandemic).
AURI, acute upper respiratory infection; Q, quarter; SMD, standardised mean difference.

50–69 years, 70 and above years) and by hypertension status (yes, no) were identified, and then the matching weight method was performed on each subset sample. Proceeding forward with each subset weighted sample, all previously mentioned steps for the main analysis were then repeated. All analysis were performed using R for windows.

RESULTS

As shown in figure 1, the COVID-19 cohort included 173 432 patients, the AURI pandemic cohort included 126 392 patients and the AURI prepandemic cohort included 352 201 patients, respectively. After matching, the sample sizes were: COVID-19 (n=102 227) versus AURI pandemic (n=102 101); COVID-19 (n=169 687) versus AURI pre pandemic (n=169 486); and AURI pandemic (n=126 392) versus AURI pre pandemic (n=126 394). As shown in tables 1–3, for each comparison, baseline covariates were well balanced post matching. For the COVID-19 versus AURI pandemic comparison, both cohorts were approximately 63% women and roughly 71% white. For the COVID-19 versus AURI prepandemic comparison, both cohorts were approximately 49% women and roughly 65% white. Last, for the AURI pandemic versus AURI prepandemic comparison, both cohorts were approximately 58% women and 74% white.

Table 4 lists the results of incident AF comparison among the study cohorts. Patients with COVID-19 were observed to have a significantly higher rate of 12-month incident AF as compared with AURI pandemic cohort (2.2% vs 1.2%, p<0.001). The odds of having incident AF were 83% higher among patients with COVID-19 as compared with AURI pandemic patients (OR 1.83; 95% CI 1.72 to 1.95).

Similar results were observed when comparing the COVID-19 cohort with the AURI prepandemic cohort, with a significantly higher rate of AF incidence observed among patients with COVID-19 as compared with patients in the AURI prepandemic cohort (2.7% vs 1.6%, p<0.001). Results from regression analysis revealed patients with COVID-19 to have 70% higher odds of experiencing incident AF in the subsequent 12-month period post diagnosis as compared with patients with AURI in the prepandemic period (OR 1.70; 95% CI 1.63 to 1.78). No significant difference in AF incidence was observed among the AURI pandemic and prepandemic cohort (1.1% vs 1.2%; OR 0.95; 95% CI 0.90 to 1.01).

Results from subanalysis by sex are shown in table 5. Across both men and women, a significantly higher rate of 12-month incident AF was observed for patients in the COVID-19 cohort as compared with those in the AURI pandemic (women: 2.0% vs 1.1%, p<0.001, OR 1.76, 95% CI 1.61 to 1.93; men: 2.5% vs 1.3%, p<0.001, OR 1.92, 95% CI 1.75 to 2.10) and AURI prepandemic cohort (women: 2.5% vs 1.5%, p<0.001, OR 1.68, 95% CI 1.58 to 1.79; men: 2.5% vs 1.3%, p<0.001, OR 1.75, 95% CI 1.65 to 1.86), respectively. For both women and men, no significant differences in AF incidence were observed among AURI pandemic and AURI prepandemic cohort, respectively.

Table 6 depicts the results of subanalysis by age. Among patients aged 21–49 years, a significantly higher risk of incident AF was observed among patients with COVID-19 as compared with AURI pandemic (0.2% vs 0.1%, p<0.001, OR 2.02, 95% CI 1.48 to 2.75) or AURI prepandemic patient cohorts (0.2% vs 0.1%, p<0.001, OR 1.70, 95% CI 1.36 to 2.14). Similar results were observed for patients aged 50–69 years and 70 years and above, respectively.

Shown in online supplemental table 1 are the results from our final subanalysis (subset by hypertension status). Among those with hypertension, we observed greater risk of incident AF among patients with COVID-19 as compared with those with AURI during the pandemic era (4.1% vs 2.5%, p<0.001, OR 1.72, 95% CI 1.60 to 1.85). A significantly greater risk of incident AF was also observed among patients with COVID-19 without hypertension as compared with patients with AURI without hypertension during the pandemic era (1.0% vs 0.5%, p<0.001, OR 2.25, 95% CI 1.98 to 2.56).

DISCUSSION

To our knowledge, this is the first study to examine the risk of incident AF among patients with COVID-19 treated in both acute and non-acute care settings. Further, our study used patients with upper respiratory infections as comparators to better reflect the unique association of SARS-CoV-2 viral infection and AF incidence. Between

Table 2 Sample characteristics of patients with COVID-19 and patients with acute upper respiratory infection (pre pandemic)

	Pre match			Post match		
	COVID-19	AURI (pre pandemic)		COVID-19	AURI (pre pandemic)	
	n=174 432	n=352 201	SMD	n=169 687	n=169 486	SMD
Age (categorical)			0.186			0.001
21–49	57 879 (33.2%)	146 578 (41.6%)		57 674 (34.0%)	57 648 (34.0%)	
50–69	61 618 (35.3%)	116 991 (33.2%)		60 019 (35.4%)	59 928 (35.4%)	
70 and above	54 935 (31.5%)	88 632 (25.2%)		51 994 (30.6%)	51 911 (30.6%)	
Gender—male	89 596 (51.4%)	144 640 (41.1%)	0.208	85 792 (50.6%)	85 780 (50.6%)	0.001
Geographic region			0.141			0.003
Northeast	25 453 (14.6%)	38 713 (11.0%)		23 722 (14.0%)	23 585 (13.9%)	
Midwest	45 358 (26.0%)	82 217 (23.3%)		44 264 (26.1%)	44 127 (26.0%)	
South	73 042 (41.9%)	160 180 (45.5%)		71 632 (42.2%)	71 764 (42.3%)	
West	30 579 (17.5%)	71 091 (20.2%)		30 069 (17.7%)	30 010 (17.7%)	
Race			0.22			0.002
Asian	6451 (3.7%)	14 683 (4.2%)		6401 (3.8%)	6418 (3.8%)	
Black	20 906 (12.0%)	33 453 (9.5%)		19 968 (11.8%)	19 887 (11.7%)	
Hispanic	31 573 (18.1%)	40 260 (11.4%)		28 911 (17.0%)	28 812 (17.0%)	
Unknown	3427 (2.0%)	6469 (1.8%)		3358 (2.0%)	3374 (2.0%)	
White	112 075 (64.3%)	257 336 (73.1%)		111 049 (65.4%)	110 995 (65.5%)	
Education≥bachelor's degree	29 916 (17.2%)	78 420 (22.3%)	0.129	29 739 (17.5%)	29 765 (17.6%)	0.001
Annual household income			0.167			0.003
<US$50k	61 028 (35.0%)	100 184 (28.4%)		57 905 (34.1%)	57 656 (34.0)	
US$50k–US$99k	52 116 (29.9%)	122 581 (34.8%)		59 991 (35.4%)	59 860 (35.3)	
≥US$100k	61 288 (35.1%)	129 436 (36.8%)		51 791 (30.5%)	51 971 (30.7)	
Elixhauser Score category			0.211			0.002
0	59 943 (34.4%)	137 607 (39.1%)		59,6034 (35.1%)	59 417 (35.1%)	
1–3	75 513 (43.3%)	164 273 (46.6%)		74 694 (44.0%)	74 640 (44.0%)	
4+	38 976 (22.3%)	50 321 (14.3%)		35 389 (20.9%)	35 430 (20.9%)	
CHA_2DS_2–VASc Score			0.193			0.001
0	39 245 (22.5%)	74 221 (21.1%)		38 931 (22.9%)	38 858 (22.9%)	
1–3	94 873 (54.4%)	220 822 (62.7%)		94 635 (55.8%)	94 518 (55.8%)	
4+	40 314 (23.1%)	57 158 (16.2%)		36 122 (21.3%)	36 111 (21.3%)	
Congestive heart failure—yes	9212 (5.3%)	9146 (2.6%)	0.138	7626 (4.5%)	7598 (4.5%)	0.001
Valvular disease—yes	8929 (5.1%)	14 768 (4.2%)	0.044	8416 (5.0%)	8484 (5.0%)	0.002
Obesity—yes	27 850 (16.0%)	43 835 (12.4%)	0.101	26 091 (15.4%)	26 124 (15.4%)	0.001
Diabetes—yes	38 788 (22.2%)	51 398 (14.6%)	0.198	35 483 (20.9%)	35 449 (20.9%)	<0.001
Hypertension—yes	78 471 (45.0%)	130 080 (36.9%)	0.164	74 469 (43.9%)	74 428 (43.9%)	0.001
Pulmonary circulation disorders—yes	2944 (1.7%)	3493 (1.0%)	0.061	2577 (1.5%)	2572 (1.5%)	<0.001
Peripheral vascular disease—yes	18 394 (10.5%)	21 230 (6.0%)	0.164	16 132 (9.5%)	16 138 (9.5%)	<0.001
Obstructive sleep apnoea—yes	14 344 (8.2%)	23 628 (6.7%)	0.058	13 619 (8.0%)	13 730 (8.1%)	0.003
Hyperthyroidism—yes	977 (0.6%)	1771 (0.5%)	0.008	931 (0.5%)	921 (0.5%)	0.001
Prior history of cardiac surgery—yes	2591 (1.5%)	3711 (1.1%)	0.039	2395 (1.4%)	2425 (1.4%)	0.002
Alcohol-related disorders—yes	2523 (1.4%)	3754 (1.1%)	0.034	2294 (1.4%)	2296 (1.4%)	<0.001
Congenital heart disease—yes	888 (0.5%)	1566 (0.4%)	0.009	837 (0.5%)	856 (0.5%)	0.002

AURI, acute upper respiratory infection; SMD, standardised mean difference.

Table 3 Sample characteristics of patients with acute upper respiratory infection pre pandemic and pandemic

	Pre match			Post match		
	AURI (pre pandemic)	AURI (pandemic)		AURI (pre pandemic)	AURI (pandemic)	
	n=352 201	n=126 392	SMD	n=126 394	n=126 392	SMD
Age (categorical)			0.073			<0.001
21–49	146 578 (41.6%)	54 589 (43.2%)		54 576 (43.2%)	54 589 (43.2%)	
50–69	116 991 (33.2%)	43 901 (34.7%)		43 891 (34.7%)	43 901 (34.7%)	
70 and above	88 632 (25.2%)	27 902 (22.1%)		27 928 (22.1%)	27 902 (22.1%)	
Gender—male	144 640 (41.1%)	54 182 (42.9%)	0.036	54 176 (42.9%)	54 182 (42.9%)	<0.001
Geographic region			0.113			0.001
Northeast	38 713 (11.0%)	12 281 (9.7%)		12 282 (9.7%)	12 281 (9.7%)	
Midwest	82 217 (23.3%)	35 491 (28.1%)		35 520 (28.1%)	35 491 (28.1%)	
South	160 180 (45.5%)	53 285 (42.2%)		53 244 (42.1%)	53 285 (42.2%)	
West	71 091 (20.2%)	25 335 (20.0%)		25 348 (20.1%)	25 335 (20.0%)	
Race			0.047			0.001
Asian	14 683 (4.2%)	4152 (3.3%)		4147 (3.3%)	4152 (3.3%)	
Black	33 453 (9.5%)	12 274 (9.7%)		12 261 (9.7%)	12 274 (9.7%)	
Hispanic	40 260 (11.4%)	14 703 (11.6%)		147,16 (11.6%)	14 703 (11.6%)	
Unknown	6469 (1.8%)	2408 (1.9%)		24,11 (1.9%)	2408 (1.9%)	
White	257 336 (73.1%)	92 855 (73.5%)		92 859 (73.5%)	92 855 (73.5%)	
Education≥bachelor's degree	78 420 (22.3%)	24 755 (19.6%)	0.066	24 768 (19.6%)	24 755 (19.6%)	<0.001
Annual household income			0.068			<0.001
<US$50k	100 184 (28.4%)	39 506 (31.3%)		39 504 (31.3%)	39 506 (31.3%)	
US$50k–US$99k	122 581 (34.8%)	43 140 (34.1%)		43 731 (34.6%)	43 746 (34.6%)	
US$≥100k	129 436 (36.8%)	43 746 (34.6%)		43 159 (34.1%)	43 140 (34.1%)	
Elixhauser Score category			0.036			<0.001
0	137 607 (39.1%)	49 779 (39.4%)		49 775 (39.4%)	49 779 (39.4%)	
1–3	164 273 (46.6%)	57 160 (45.2%)		57 171 (45.2%)	57 160 (45.2%)	
4+	50 321 (14.3%)	19 453 (15.4%)		19 449 (15.4%)	19 453 (15.4%)	
CHA_2DS_2–VASc Score			0.052			<0.001
0	74 221 (21.1%)	28 781 (22.8%)		28 775 (22.8%)	28 781 (22.8%)	
1–3	220 822 (62.7%)	78 915 (62.4%)		79 641 (63.0%)	79 627 (63.0%)	
4+	57 158 (16.2%)	18 696 (14.8%)		17 979 (14.2%)	17 984 (14.2%)	
Congestive heart failure—yes	9146 (2.6%)	3371 (2.7%)	0.004	3375 (2.7%)	3371 (2.7%)	<0.001
Valvular disease—yes	14 768 (4.2%)	4771 (3.8%)	0.021	4769 (3.8%)	4771 (3.8%)	<0.001
Obesity—yes	43 835 (12.4%)	17 222 (13.6%)	0.035	17 235 (13.6%)	17 222 (13.6%)	<0.001
Diabetes—yes	51 398 (14.6%)	17 878 (14.1%)	0.013	17 884 (14.1%)	17 878 (14.1%)	<0.001
Hypertension—yes	130 080 (36.9%)	44 917 (35.5%)	0.029	44 901 (35.5%)	44 917 (35.5%)	<0.001
Pulmonary circulation disorders—yes	3493 (1.0%)	1351 (1.1%)	0.008	1350 (1.1%)	1351 (1.1%)	<0.001
Peripheral vascular disease—yes	21 230 (6.0%)	7829 (6.2%)	0.007	7824 (6.2%)	7829 (6.2%)	<0.001
Obstructive sleep apnoea—yes	23 628 (6.7%)	9466 (7.5%)	0.03	9480 (7.5%)	9466 (7.5%)	<0.001
Hyperthyroidism—yes	1771 (0.5%)	608 (0.5%)	0.003	607 (0.5%)	608 (0.5%)	<0.001
Prior history of cardiac surgery—yes	3711 (1.1%)	1241 (1.0%)	0.007	1245 (1.0%)	1241 (1.0%)	<0.001
Alcohol-related disorders—yes	3754 (1.1%)	1862 (1.5%)	0.036	1869 (1.5%)	1862 (1.5%)	<0.001
Congenital heart disease—yes	1566 (0.4%)	580 (0.5%)	0.002	581 (0.5%)	580 (0.5%)	<0.001

AURI, acute upper respiratory infection; SMD, standardised mean difference.

Table 4 Odds of incident atrial fibrillation in the 365 days post index date

Outcome	Cohort comparison % versus %	P value	OR (95% CI)
Incident atrial fibrillation*	COVID-19 versus AURI pandemic 2.2% vs 1.2%	<0.001	1.83 (1.72 to 1.95)
Incident atrial fibrillation*	COVID-19 versus AURI pre pandemic 2.7% vs 1.6%	<0.001	1.70 (1.63 to 1.78)
Incident atrial fibrillation*	AURI pre pandemic versus AURI pandemic 1.1% vs 1.2%	0.133	0.95 (0.90 to 1.01)

*Weighted regression model; covariates adjusted for: none.
AURI, acute upper respiratory infection.

2.2% and 2.7% of patients with COVID-19 in our analysis developed AF in the year following COVID-19 infection. Patients with COVID-19 were observed to be at a higher risk of developing AF as compared with patients with AURI identified in either the pandemic or prepandemic period, respectively.

Our results are consistent with prior studies that have examined an association between COVID-19 and AF.[7 14 23 24] In one such study of a large hospital system in the USA, hospitalised patients with COVID-19 were observed to have 19% higher risk (OR 1.19, 95% CI 1.00 to 1.41) of developing AF during their hospitalisation when compared with hospitalised patients without COVID-19. The authors further reported that hospitalised patients with COVID-19 had 57% higher risk of developing AF (OR 1.57, 95% CI 1.23 to 2.00) when compared with hospitalised non-COVID-19 patients during the prepandemic period. In our study, patients with COVID-19 had 83% higher risk of 12-month incident AF as compared with patients with AURI in the pandemic period and 70% higher risk as compared with patients with AURI in the prepandemic period. Further, results from our subanalysis suggest that the increased risk of AF extends to both women and men, with women having 68%–76% higher risk of AF and men having 75%–92% higher risk of AF as compared with patients with AURI. Further, subanalysis by age suggested that the increased risk of AF is not just limited to elderly individuals as patients in the 21–49 years and 50–69 years age groups were also observed to be at a higher risk. Patients with COVID-19 aged 21–49 years were more than twice as likely to be diagnosed with AF as compared with their peers in the AURI pandemic cohort and had 70% higher risk of AF as compared with AURI prepandemic cohort. Similar results were observed for patients in the 50–69 years age group. Though results for those aged 70 years and above were similar, we did observe a significant difference in the incidence of AF among AURI pandemic and prepandemic cohorts for this age group. As such, the relationship between COVID-19 and AF in this elderly cohort of patients aged 70 years and above was inconclusive. The incremental AF burden observed among young adults in our study is concerning, as the classical association between AF genesis and age skews towards older patients.

In contrast to prior studies that focused on hospitalised patients with COVID-19, our analysis of patients with COVID-19 treated in both the acute and non-acute settings suggests that the association between COVID-19 and AF may extend beyond only those patients most seriously affected by COVID-19. Our results highlight the

Table 5 Odds of incident atrial fibrillation in the 365 days post index date subset by sex at birth categories

Outcome	Cohort comparison % versus %	P value	OR (95% CI)
	COVID-19 versus AURI pandemic		
Incident atrial fibrillation (female)*	2.0% vs 1.1%	**<0.001**	1.76 (1.61 to 1.93)
Incident atrial fibrillation (male)*	2.5% vs 1.3%	<0.001	1.92 (1.75 to 2.10)
	COVID-19 versus AURI pre pandemic		
Incident atrial fibrillation (female)*	2.5% vs 1.5%	<0.001	1.68 (1.58 to 1.79)
Incident atrial fibrillation (male)*	2.9% vs 1.7%	<0.001	1.75 (1.65 to 1.86)
	AURI pandemic versus AURI pre pandemic		
Incident atrial fibrillation (female)*	1.0% vs 1.0%	0.85	0.99 (0.91 to 1.08)
Incident atrial fibrillation (male)*	1.2% vs 1.3%	0.077	0.92 (0.85 to 1.01)

*Weighted regression model; covariates adjusted for: none.
AURI, acute upper respiratory infection.

Table 6 Odds of incident atrial fibrillation in the 365 days post index date subset by age categories

Outcome	Cohort comparison % versus %	P value	OR (95% CI)
	COVID-19 versus AURI pandemic		
Incident atrial fibrillation (21–49 years)*	0.2% vs 0.1%	**<0.001**	2.02 (1.48 to 2.75)
Incident atrial fibrillation (50–69 years)*	1.8% vs 1.1%	**<0.001**	1.61 (1.44 to 1.80)
Incident atrial fibrillation (70 and above years)*	6.0% vs 3.1%	**<0.001**	1.97 (1.82 to 2.14)
	COVID-19 versus AURI pre pandemic		
Incident atrial fibrillation (21–49 years)*	0.2% vs 0.1%	<0.001	1.70 (1.36 to 2.14)
Incident atrial fibrillation (50–69 years)*	1.9% vs 1.1%	<0.001	1.68 (1.54 to 1.83)
Incident atrial fibrillation (70 and above years)*	6.3% vs 3.7%	<0.001	1.75 (1.66 to 1.84)
	AURI pandemic versus AURI pre pandemic		
Incident atrial fibrillation (21–49 years)*	0.1% vs 0.1%	0.588	0.92 (0.70 to 1.23)
Incident atrial fibrillation (50–69 years)*	1.1% vs 1.1%	0.258	1.06 (0.96 to 1.18)
Incident atrial fibrillation (70 and above years)*	3.0% vs 3.3%	0.016	0.91 (0.84 to 0.98)

*Weighted regression model; covariates adjusted for: none.
AURI, acute upper respiratory infection.

importance of heightened awareness for the potential development of AF among patients affected by COVID-19, irrespective of the extent of their severity of illness. If diagnosed, appropriate evidence-based management of AF is critical in alleviating the long-term clinical and economic burden imposed by AF.[25]

The exact mechanism(s) underlying the association between COVID-19 and incident AF remains poorly understood. Prior investigations have highlighted myocardial injury, either through systemic inflammation, damage to cardiomyocytes, hypoxia or other mechanisms, to be one of the main pathogenic features of COVID-19.[26] Others have suggested that patients with COVID-19 may experience an increased probability of developing overactivity of the sympathetic nervous system, pneumonia, acidosis and other factors that could exacerbate cardiac morbidity and induce cardiac arrhythmias.[19 22 27–30] However, considering that our study patients with COVID-19 had a higher risk of AF as compared with those with an AURI, it is conceivable that infectivity with the SARS-CoV-2 virus generates an inflammatory process at the myocardial level that triggers AF within diverse populations.[31–33] Further research is needed to better understand whether this association persists across other patient populations, while also investigating more deeply the potential underlying mechanisms responsible for this association.

Limitations

We acknowledge several limitations to our study. There exists the possibility of patients having COVID-19 infection and/or an AURI without seeking formal medical care, thereby introducing misclassification bias into our analysis. This is an especially important consideration given recent estimates such as those from a National Institutes of Health study suggesting that by the 6-month mark of the pandemic there were already roughly 17 million undiagnosed cases of COVID-19 in the USA,[34] as well as estimates from the Centers for Disease Control and Prevention (CDC) which suggest that only 1 in 4 COVID-19 infections were reported in this setting between February 2020 and September 2021.[35] However, to alleviate misclassification bias, one of our comparator cohorts included patients with AURI identified in the prepandemic period (where patients were extremely unlikely to have COVID-19). Those patients with COVID-19 were observed to have higher risk of AF as compared with the prepandemic cohort of AURI lends further evidence to suggest an association between COVID-19 and AF. Considering the use of administrative claims database in our study, coding errors during claims processing could have influenced study results.

We also acknowledge the limitations of ORs including their lack of collapsibility.[36 37]

Having said that, considering the study design, large sample size and outcome of interest (which is relatively rare (ie, <10%), our choice of measure of association was thought to be an appropriate one.[36–38] In this instance of a relatively rare outcome, ORs would also be roughly equal to risk ratios.[36 37] For the COVID-19 versus AURI pandemic comparison, we calculate risk ratio to explore this phenomenon further. The difference between the measures of association was minimal (OR: 1.83; 95% CI: 1.72 to 1.95 vs risk ratio: 1.81; 95% CI: 1.70 to 1.93). Finally, our study sample involved commercially insured patients. As such, study findings may not be generalisable to patients without commercial insurance, or those patients covered by Medicare fee-for-service insurance.

CONCLUSION

Among a commercially insured US-based population, an association exists between documented COVID-19

infection and AF incidence. Given the widespread rate of infectivity with COVID-19 across diverse populations, a potentially causal relationship between COVID-19 and incident AF is concerning. Growing numbers of AF patients are likely to place additional strain on healthcare delivery systems already impacted by the pandemic and its clinical and financial sequelae. Independent of the clinical venue of diagnosis, patients with COVID-19 were observed to have higher risk of developing AF in the 12 months post infection period when compared with patients with AURI. The results were consistent across sex, with higher risk of AF seen among both females and males with COVID-19. Furthermore, subanalysis by age revealed the incremental AF burden associated with COVID-19 to be especially pronounced among younger adults. Given the considerable prevalence of COVID-19 and its association with AF as observed in this study, social interventions aimed at promoting patient awareness of common symptoms associated with AF should be explored. Healthcare providers should consider AF assessment as part of routine evaluation even in those patients affected by COVID-19 not requiring hospitalisation. Finally, for patients who develop AF post-COVID-19 infection, timely evidence-based management of their arrhythmic condition should remain the mainstay of treatment.

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