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Annual flu shot: Does it help patients with COVID-19?

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Abstract

Aim of the study: The impact of annual flu vaccination on the patients' clinical course with COVID-19 and the outcome were tested.

Methods: A total of 149 patients with COVID-19-positive admitted from March 20 to May 10, 2020, were retrospectively enrolled.

Results: Ninety-eight (65.8%) patients received at least a single annual flu shot in the last year, and fifty-one (34.2%) were never vaccinated. On presentation, vaccinated patients were more likely to present with gastrointestinal symptoms ($P < .05$). There were no significant differences between study groups in laboratory findings or clinical outcomes. In multivariate analysis, receiving the annual shot did not influence risk of intensive care unit admission (OR = 1.17, 95%CI = 0.50-2.72, $P = .72$), intubation (OR = 1.40, 95%CI = 0.60-3.23, $P = .43$), complications (OR = 1.08, 95%CI = 0.52-2.26, $P = .83$) or mortality (OR = 1.29, 95%CI = 0.31-5.29, $P = .73$).

Conclusion: Although the benefits of the influenza vaccine for preventing disease and reducing morbidity in influenza patients are well established, no differences in outcomes for hospitalised patients with COVID-19 who received their annual influenza vaccination versus the non-vaccinated cohort were evident. There is a need for future meta-analyses, including randomised controlled studies in which the number of cases is increased to validate these findings.

1 | INTRODUCTION

The pandemic of coronavirus disease 2019 (COVID-19) has been overwhelming healthcare systems worldwide.[1] With the influenza season approaching, the Centers for Disease Control and Prevention (CDC) will be recommending annual influenza vaccinations to prevent the spread of another potentially deadly respiratory virus. The COVID-19 pandemic began in the United States, and much of the world towards the end of the traditional "flu season". In Louisiana, the first COVID-19 case was identified on March 9, 2020, and the outbreak grew particularly fast relative to other states.[2] Although extensive mitigation efforts were applied, New Orleans, Louisiana, had the highest per capita COVID-19-related mortality rate in the nation – "twice that of New York City and four times the rate in

Seattle".[2,3] The flu season begins in October, peaks most often in February and can continue into May.[4] Thus, investigating the relationship between COVID-19 patients' clinical course and receiving the 2019-2020 influenza vaccine has been limited.

The pursuit of a novel COVID-19 vaccine occupies many laboratories around the world. It serves as a reminder of how accustomed the modern world was to the annual influenza vaccine to prevent viral respiratory illness. Following the influenza pandemic of 1918, years of work isolating the virus, growing it in hen eggs, and inactivating it with formalin birthed the inactivated annual vaccine.[5] US manufacturers estimate the production and distribution of influenza vaccines to be 194-198 million in the 2019-2020 flu season. The concurrent COVID-19 pandemic warrants investigation into the effects, if any, receiving the vaccination had during the 2019-2020 season.

Previous research has suggested an association between receiving the flu vaccine and an increased rate of contracting non-influenza viral respiratory illnesses (NIRVs) such as rhinoviruses, adenoviruses and coronaviruses.[6,7] A proposed mechanism is virus interference, meaning that a natural influenza infection will provide temporary, non-specific immunologic resistance to NIRVs. Cowling et al found an increased risk of contracting a serologically confirmed NIRV in children who had received the trivalent influenza vaccine.[8]

Nevertheless, other research demonstrated no relationship between being vaccinated and increased NIRVs.[9-11] A large study of military personnel in the United States demonstrated mixed results, concluding that influenza vaccination status did not increase a person's overall risk of an NIRV. However, in that study, vaccinated patients had an overall increased rate of coronavirus infections.[12]

Common NIRVs have historically not been associated with severe morbidity or hospitalisations. Therefore, there are limited data on the effects of influenza vaccination and disease course in these patients. Although the influenza vaccine demonstrates benefit in patients hospitalised with acute respiratory illness caused by influenza, the impact on patients with COVID-19 is not known.[13] The purpose of this study is to evaluate the impact of annual influenza vaccination on the disease course and outcomes of COVID-19 in a cohort of patients with COVID-19-positive. We hypothesise that patients who received the influenza vaccine might have a more favourable immune response to COVID-19. Our outcome measures include initial presentation, laboratory values at admission, and hospital course (ie, intensive care unit [ICU] admission, need for mechanical ventilation, length of stay), disease complications and in-hospital mortality rate.

2 | METHODS

2.1 | Study population

This is a retrospective study performed after acquiring Tulane University's institutional review board (IRB) approval. Data were collected on all patients with COVID-19-positive who had been admitted from March 20, 2020, to May 10, 2020, to Tulane Medical Center and University Medical Center, New Orleans. These dates were selected because the first cases of COVID-19 in New Orleans in mid-March, and these separate medical centres were some of the first in Louisiana to treat patients with COVID-19. Demographics, underlying comorbidities, clinical presentation, laboratory values, and outcome data were collected using REDCap (Research Electronic Data Capture) electronic data capture tool. REDCap is a secure, web-based software platform designed to support data capture for research studies. Patients were divided into two groups: one who received the annual flu shot within 1 year and those who did not receive the annual flu shot. Patients underwent a flu swab and had negative flu results at the time of presentation. Patients were excluded from analysis if they had no data regarding their flu vaccination status.

2.2 | Outcomes

A comparison between the vaccinated and unvaccinated patients was performed. The primary outcome was in-hospital mortality. Secondary outcomes were symptoms on initial presentation, ICU admission, need for mechanical ventilation and length of hospital stay. Prolonged intubation was defined when taking >2 days, and prolonged hospital stay was defined when staying in hospital >7 days. Clinical diagnosis of complications was made using standard definitions such as the Risk, Injury, Failure, Loss of Kidney Function, and End-stage kidney disease (RIFLE) score for renal injury. Berlin criteria were also used to identify patients with acute respiratory distress syndrome (ARDS).

2.3 | Statistical analysis

Data management was performed using SAS v9.4, while SPSS v26.0 was used for statistical analysis. χ^2 and Fisher's exact tests were applied for categorical variables. Student's t-test and Mann–Whitney U-test were applied for parametric and non-parametric continuous variables, respectively, according to data distribution checked by the Shapiro–Wilk test. The two-sided P-value was set to be significant at <.05. Using the G*Power tool (version 3.1.9.2.) at the specified sample size for each study group, the medium effect size = 0.5, and alpha error probability = 0.05, the estimated study power was 82%. Multiple regression analysis was iterated using binary logistic regression models for all outcomes and cox hazard proportionate regression model for survival, adjusted by age, sex, obesity and neuropsychiatric comorbidity.

3 | RESULTS

This study included 149 patients with COVID-19-positive, 98 (65.8%) received at least a single annual flu shot in the last year, and 51 (34.2%) were never vaccinated against the annual flu. Table 1 summarises the demographics and clinical characteristics of patients with COVID-19 at admission. Of note, patients' mean age, body mass index (BMI), and comorbid conditions were similar between groups. There were more women in the vaccinated group (66, 67.3%) compared with the unvaccinated group (21, 41.2%) ($P = .003$). On presentation, vaccinated patients were more likely to present with gastrointestinal symptoms such as nausea, vomiting and diarrhoea ($P = .028$). The most common chief complaint was shortness of breath, which occurred in 30 (58.8%) of unvaccinated patients and 55 (56.1%) in vaccinated patients. On clinical assessment, there were no differences between groups in terms of vital signs or severity of COVID-19 disease (all vital sign P-values > .05).

Table 2 summarises the laboratory findings between groups on admission. There were no significant differences in arterial blood glass, complete blood count, complete metabolic panel, and glycaemic profile between vaccinated and unvaccinated COVID-19 patients.

TABLE 1 Demographic and clinical characteristics of patients with COVID-19 at admission

Characteristics		Unvaccinated (n = 51)	Vaccinated (n = 98)	P-value
Demographic data		# (%)	# (%)	
Age	Mean ±SD	56.67 ± 17.84	59.51 ± 14.86	.30
	18-49 years	16 (31.4)	19 (19.8)	.29
	50-64 years	18 (35.3)	38 (39.6)	
	≥ 65 years	17 (33.3)	39 (40.6)	
Sex	Female	21 (41.2)	66 (67.3)	.003
	Male	30 (58.8)	32 (32.7)	
Race	African-American	38 (74.5)	73 (74.5)	.07
	White	13 (25.5)	17 (17.3)	
	Not reported	0 (0)	8 (8.2)	
BMI, kg/m^2	Mean ±SD	32.56 ± 7.28	33.61 ± 9.21	.49
Smoking	None	29 (56.9)	69 (70.4)	.24
	Past smoker	19 (37.3)	26 (26.5)	
	Current smoker	3 (5.9)	3 (3.1)	
Chief complaints				
Asymptomatic	Asymptomatic	5 (9.8)	13 (13.3)	.53
Non-specific	Fever	14 (27.5)	14 (14.3)	.07
	Fatigue/weakness	4 (7.8)	10 (10.2)	.77
	Myalgia/FLS	4 (7.8)	8 (8.2)	.95
	Headache	0 (0)	3 (3.1)	.55
Respiratory symptoms	Shortness of breath	30 (58.8)	55 (56.1)	.86
	Cough	7 (13.7)	15 (15.3)	.80
	Chest pain	2 (3.9)	4 (4.1)	.96
GIT symptoms	Nausea, vomiting, diarrhoea	0 (0)	9 (9.2)	.028
Comorbidities				
Presence of comorbidities	Not present	5 (9.8)	8 (8.2)	.74
	Present	46 (90.2)	90 (91.8)	
Type of comorbidities	Obesity	34 (66.7)	53 (54.1)	.16
	Hypertension	33 (64.7)	74 (75.5)	.18
	Diabetes	18 (35.3)	45 (45.9)	.23
	Chronic heart failure	4 (7.8)	10 (10.2)	.77
	Arrhythmia	3 (5.9)	7 (7.1)	.76
	Coronary artery disease	4 (7.8)	13 (13.3)	.42
	Asthma	9 (17.6)	12 (12.2)	.46
	COPD	9 (17.6)	7 (7.1)	.09
	Chronic kidney disease	9 (17.6)	14 (14.3)	.64
	Cerebrovascular disease	5 (9.8)	12 (12.2)	.79
	Psychiatric disorders	16 (31.4)	39 (39.8)	.37
	Cancer	7 (13.7)	21 (21.4)	.28
Clinical assessment				
Severity	qSOFA score	0.81 ± 0.81	0.68 ± 0.71	.47
	CURB65 score	1.42 ± 1.12	1.49 ± 1.25	.83
Orientation	Glasgow coma score	13.81 ± 2.82	13.95 ± 2.57	.83
Vital signs	Temperature (°F)	99.14 ± 1.50	99.35 ± 1.51	.46
	Pulse rate (BPM)	86.85 ± 15.19	88.00 ± 17.32	.72

(Continues)

TABLE 1 (Continued)

Characteristics		Unvaccinated (n = 51)	Vaccinated (n = 98)	P-value
	Systolic blood pressure (mmHg)	120.22 ± 16.01	126.33 ± 20.84	.10
	Diastolic blood pressure (mmHg)	68.54 ± 12.75	72.18 ± 12.85	.14
	Mean arterial pressure (mmHg)	101.80 ± 15.52	107.23 ± 17.85	.10
	Respiratory rate (BrPM)	20.37 ± 4.75	21.41 ± 5.65	0.31

Note: Data are presented as mean and standard deviation or frequency and percentage.

Psychiatric disorders include depression, schizophrenia, and anxiety disorders. χ^2, Fisher's exact, or Student's *t*-tests were used. *P*-value at < .05 was considered significant.

Abbreviations: BMI, body mass index; FLS, Flu-like symptoms; GIT, gastrointestinal tract; NA, not applicable.

TABLE 2 Results of investigations on admission

Characteristics		Unvaccinated (n = 51)	Vaccinated (n = 98)	P-value
ABG findings	SaO$_2$ (%)	94.36 ± 5.15	94.33 ± 4.42	.97
	pH respiratory	7.40 ± 0.10	7.43 ± 0.06	.21
	PaCO$_2$ (mmHg)	38.25 ± 12.50	35.16 ± 6.93	.27
	PaO$_2$ (mmHg)	69.91 ± 15.32	69.65 ± 30.48	.97
	Anion gap (mM)	16.22 ± 23.87	11.69 ± 3.27	.19
	Lactic acid (mmol/L)	3.40 ± 3.20	6.06 ± 10.04	.68
	HCO$_3$ (mmol/L)	25.44 ± 3.75	24.81 ± 3.27	.55
	FiO$_2$ (%)	35.59 ± 26.20	37.75 ± 28.21	.79
	PaO$_2$/FiO$_2$ ratio	256.29 ± 115.80	253.44 ± 113.83	.93
Complete blood picture	White blood cells (10^9/L)	8.6 (5.8-11.9)	6.8 (5.5-8.7)	.21
	Haemoglobin (g/dL)	11.8 (11.1-13.2)	12.2 (10.3-13.3)	.98
	Haematocrit (%)	36.4 (34.1-39.9)	37.2 (31.8-38.9)	.79
	Platelet count (10^9/L)	207.5 (169.5-259.5)	201 (158-274)	.41
	Neutrophil count (10^9/L)	6.2 (4-8.9)	4.9 (3.8-6.8)	.24
	Lymphocyte count (10^9/L)	1 (0.7-1.4)	0.9 (0.8-1.5)	.38
	Neutrophil lymphocyte ratio	5.4 (3-9.5)	5.1 (3.1-9.7)	.03
Electrolytes	Serum sodium (mm/L)	138 (135-140.5)	138 (135-140)	.19
	Serum potassium (mm/L)	4.3 (3.8-4.6)	3.9 (3.6-4.4)	.07
	Serum chloride (mm/L)	100.5 (99-108.8)	101 (97-105)	.60
	Calcium corrected (mg/dL)	9.1 (8.9-9.6)	9.1 (8.7-9.5)	.27
Glycaemic profile	Random blood sugar (mg/dL)	106.5 (94.5-157.8)	115 (96-148)	.74
	HbA1c (%)	6.3 (5.8-6.5)	8.5 (5.7-12.1)	.20
Renal function test	Blood urea nitrogen (mg/dL)	24 (11.5-34.8)	18 (10-27)	.84
	Serum creatinine (mg/dL)	1.4 (0.9-3.9)	1 (0.8-1.5)	.73
Liver function test	Total protein (g/dL)	6.8 (6.2-7.5)	6.8 (6.3-7.2)	.84
	Albumin (g/dL)	3.1 (2.7-3.6)	3.2 (2.9-3.6)	.51
	Bilirubin (mg/dL)	0.5 (0.3-0.6)	0.5 (0.4-0.6)	.55
	Alkaline phosphatase (U/L)	66.5 (51.3-100.5)	63 (54-79)	.14
	AST (U/L)	37.5 (19.3-47.3)	38 (26-47)	.96
	ALT (U/L)	15.5 (11.3-34.8)	25 (18-31)	.55

Note: Data are presented as mean and standard deviation (SD), median and interquartile range or frequency and percentage.

χ^2, Fisher's exact, or Mann–Whitney *U*-tests were used. *P*-value at <.05 was considered significant.

Abbreviations: ALT, alanine transaminase; AST, Aspartate transaminase; FiO2, Fraction of inspired oxygen; HbA1c, glycosylated haemoglobin; HCO3, bicarbonate; PaCO2, partial pressure of carbon dioxide; PaO2, partial pressure of oxygen; SaO2, oxygen saturation.

TABLE 3 Outcomes of vaccinated and unvaccinated patients with COVID-19

Characteristics		Unvaccinated (n = 51)	Vaccinated (n = 98)	P-value
ED disposition	Floor	39 (76.5)	73 (74.5)	.84
	ICU	12 (23.5)	25 (25.5)	
Procedures	Mechanical ventilation	7 (13.7)	27 (27.6)	.57
	Require intubation	11 (21.6)	28 (28.6)	.43
	Extubation	10 (19.6)	18 (18.4)	.13
Develop complications	Negative	30 (58.8)	57 (58.2)	.93
	Positive	21 (41.2)	41 (41.8)	
Type of complications	ARDS	10 (19.6)	20 (20.4)	.91
	Unplanned reintubation	1 (1.96)	4 (4.1)	.63
	Sepsis	4 (7.8)	16 (16.3)	.21
	Acute kidney injury	13 (25.5)	21 (21.4)	.68
Mortality	Alive	48 (94.1)	88 (89.8)	.54
	Dead	3 (5.9)	10 (10.2)	
Death location	Floor	1 (2.0)	9 (9.2)	.10
	ICU	2 (3.9)	1 (1.0)	
Duration, days	Intubation days	1 (0.5-2)	5 (2.3-6.8)	.14
	Ventilation days	6 (3-12)	5 (4-7.8)	.12
	Total LOS	21 (13.5-26.5)	18 (12.3-26)	.92
	ICU LOS	7 (5.5-19.5)	10 (8-12.5)	.09
	Time to death	13 (6-0)	8 (5.5-10.3)	.37

Note: Data are presented as median and interquartile range or frequency and percentage. Fisher's exact or Mann–Whitney *U*-tests were used. *P*-value at <.05 was considered significant.

Abbreviations: AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; ED, emergency department; ICU, intensive care unit; LOS, length of stay.

The clinical outcomes of 149 patients with COVID-19 are summarised in Table 3. A total of 34 (22.8%) were initially mechanically ventilated, 39 (26.2%) were intubated during their hospital stay and 28 (18.7%) were subsequently extubated. 37 (24.8%) required an ICU admission, whereas most patients received care on the general medicine wards. The complication rate for all patients with COVID-19 was high (41.6%). Specifically, the development of ARDS occurred in 30 (20.1%) patients, sepsis occurred in 20 (13.4%) patients and acute kidney injury (AKI) occurred in 34 (22.8%) patients. 13/149 (8.7%) died from COVID-19. No significant differences in clinical outcomes, including mortality between vaccinated and unvaccinated patients, were found.

Binary logistic regression analysis was performed, which adjusted data by age, gender and body mass index (Figure 1). These results demonstrated no significant differences between vaccinated and unvaccinated patients in ICU admission, intubation, complications (AKI, ARDS, sepsis), prolonged intubation (greater than or equal to 2 days), prolonged hospital stay (greater than or equal to 7 days) or mortality.

4 | DISCUSSION

The unfortunate trajectory of the COVID-19 pandemic is almost certain to continue into the 2020-2021 influenza season this fall, and many questions remain about the relationship between these two respiratory pathogens. Although the influenza vaccine has proven efficacious in reducing influenza cases in children, adults and the elderly people and preventing serious complications in critically ill flu patients, it is unknown what effect the vaccine has on COVID-19 patients' disease course.[13-16]

Our study had a few limitations. Firstly, our study population was limited to one geographic area in the South-eastern United States, with data from two hospitals. Secondly, because of the retrospective nature of this study, information about patients' influenza vaccination status for the 2019-2020 season was limited because of the differing electronic medical records used. As well, there was no information gathered on the type of influenza vaccine received.

We hypothesised that patients who received the influenza vaccine might have a more favourable immune response to COVID-19.
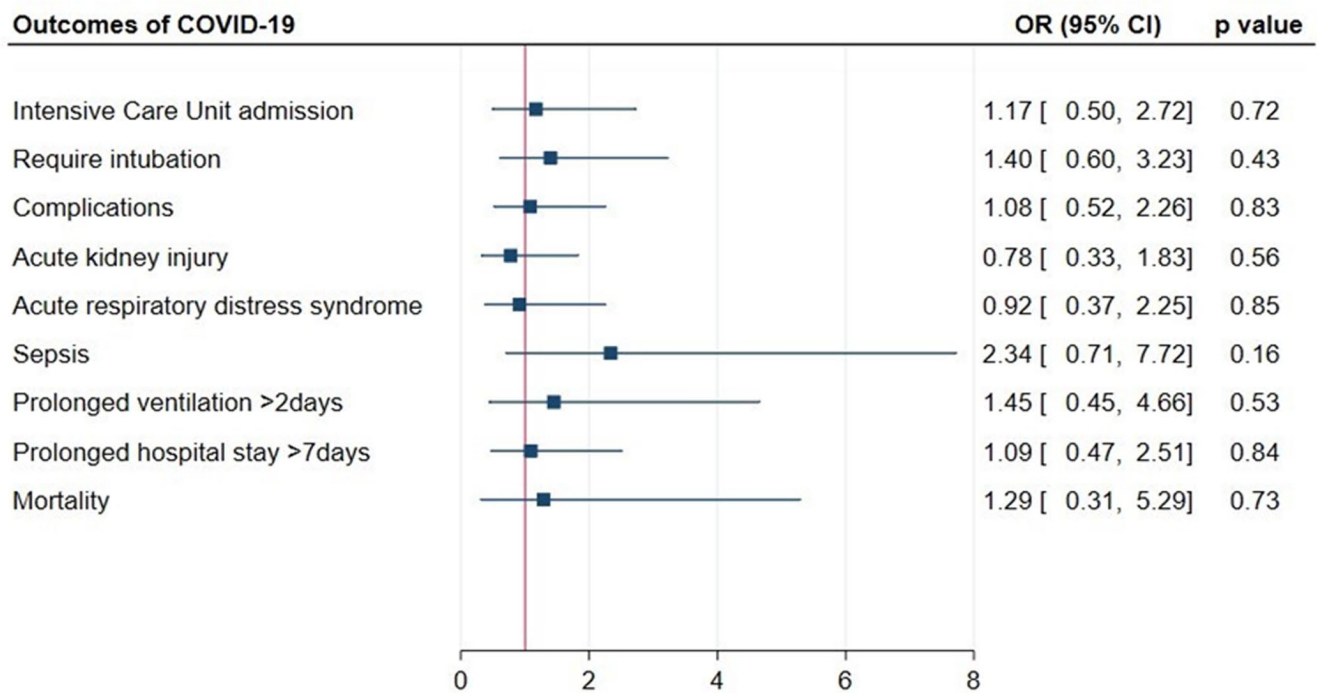
FIGURE 1 Binary logistic regression analysis of annual flu shot on COVID-19 outcomes adjusted by age, sex and body mass index. OR (95% CI): Odds ratio (95% confidence interval)

However, our study of hospitalised patients with COVID-19 found no improved or worsened outcomes in the vaccinated versus unvaccinated populations. The greatest interest outcomes were ICU length of stay, days receiving ventilation, development of an AKI, meeting sepsis criteria, developing ARDS, hospital length of stay and mortality. This suggests no protective or harmful impact from receiving the 2019-2020 flu shot in more severe COVID-19 disease.

A possible explanation for our results includes the differences in the baseline characteristics between vaccinated and unvaccinated patients. Although not statistically significant, there may have been clinical significance in the difference in comorbid conditions between groups. Our vaccinated cohort was more likely to be diabetic. Additionally, the haemoglobin A1c in our vaccinated group was 8.5%, whereas it was 6.3% in our non-vaccinated group. The comorbid condition of diabetes has been associated with significantly worse outcomes in patients with COVID-19.[17,18]

Moreover, older age has been associated with worse outcomes with COVID-19.[19] Our baseline demographics reported that 40.6% of the vaccinated patients were more than 65 years old, whereas 33.3% of the unvaccinated were more than 65 years old. Similarly, these baseline characteristics could have skewed the potential positive impacts of the influenza vaccine on COVID-19.

Regarding outcomes, a slightly higher percentage of vaccinated individuals received mechanical ventilation, developed complications and died compared with the unvaccinated group. This difference was not statistically significant, and we believe that this could be attributed to the higher comorbid conditions and older age of our vaccinated cohort. Although no difference in outcomes was demonstrated because of vaccination status, all the patients studied were COVID-19 positive; therefore, no statement can be made about the effect vaccination may have on contracting COVID-19. More future research should be conducted during the 2020-2021 influenza season to evaluate both differences in outcomes for patients with COVID-19 and the incidence of COVID-19 in vaccinated versus unvaccinated populations. Furthermore, there is a need for future metanalyses, including randomised controlled studies in which the number of cases is increased to validate the study findings.

5 | CONCLUSIONS

The benefits of the influenza vaccine for preventing disease spread and reducing morbidity in influenza patients are well established. However, our study showed no differences in key outcomes for hospitalised patients with COVID-19 who received their annual influenza vaccination. The 2020-2021 influenza vaccine is recommended for all individuals without a contraindication and should be prospectively studied in large-scale, multicentre studies to evaluate any impact on the overall COVID-19 disease burden.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

All datasets presented in this study are included in the article.

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