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TANAFFOS

Accounting for Potential Unmeasured Confounding in the Association between Influenza vaccination and COVID-19 Hospitalization: Sensitivity Analysis Using E-value Method

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Background: Unmeasured confounding is the primary obstacle to causal inference in observational research. We aimed to illuminate the association between exposure to influenza vaccination (IV) within six months before contracting the coronavirus disease (COVID-19) and COVID-19 hospitalization in relation to unmeasured confounding using the E-value method.

Materials and Methods: Information about 367 patients, 103 of whom (28.07 %) had received IV, and confounders included sex, age, occupation, cigarette smoking, opium, and comorbidities were collected. We estimated the interest association using the inverse probability weighted (IPW) method. There was no information on some potential unmeasured confounders, such as socio-economic status. Therefore, we computed E-value as a sensitivity analysis, which is the minimum strength of unmeasured confounding to explain away an exposure-outcome association beyond the measured confounders completely.

Results: IPW denoted 1.12 (95% CI: 0.71 to 1.29) times greater risk of COVID-19 hospitalization in patients exposed to IV than in unexposed individuals. Sensitivity analysis demonstrated that an E-value (95% CI) of 1.49 (1.90 to 2.15) is required to shift the RR and the corresponding confidence Interval (CI) lower and upper limits toward the null. Moreover, if they had been omitted, the most computed E-values for measured confounders were relatively larger than for unmeasured confounders.

Conclusion: According to the context of the measured confounders, if they had been omitted, an E-value of 1.16 to 1.76, a weaker confounding could fully explain away the reported association, suggesting that no relationship exists between IV and COVID-19 hospitalization.

Key words: Influenza vaccine, COVID-19, Hospitalization, Confounding variables, Sensitivity analysis

INTRODUCTION

Coronavirus disease (COVID-19) is an infectious disease caused by the severe acute respiratory coronavirus (SARS-COV-2)(1), which affected over 34,248,054 Million individuals worldwide and resulted in an estimated 607,684 deaths by July 2021(2). Since COVID-19 and influenza viruses are both enveloped RNA viruses with similar routes of entry, transmission patterns, and clinical features (3), it has been sparked an ongoing debate as to whether influenza vaccination (IV) may decrease the risk

of COVID-19 hospitalization or mortality (1, 3) through vaccine-induced innate immunity strengthening (1).

While IV has a specific relative advantage against influenza, some authors have stated that the risk of contracting non-influenza respiratory viruses may be reduced through a non-specific immunity induced by natural influenza infection in a cross-reactivity pattern (4, 5). On the contrary, some researchers have concluded that IV may lead to virus interference and thus can increase the risk of infection with other respiratory viruses in vaccinated individuals since they do not acquire non-specific immunity induced by natural infection (6-8).

Nonetheless, a few studies have proposed a protective effect for IV coverage against COVID-19 hospitalization or mortality at individual (3, 9), cross-country (10), and regional (11), and country levels (12). The unmeasured confounding bias, however, is a primary concern for the credibility of the reported association in such observational studies (13). For instance, socioeconomic status or wearing a face mask, which were not considered in the studies mentioned above, seems to be a strong common factor related to both the exposure and outcome, which may explain indicated association. More specifically, socioeconomic status can influence IV coverage and might predict COVID-19 hospitalization. Similarly, those wearing face masks may take IV vaccination more seriously and be less frequently hospitalized due to COVID-19. To confirm causation, sensitivity analysis is used to assess how the association between IV coverage and COVID-19 hospitalization can still be strong in the presence of potential unmeasured confounders. The E-value method, a sensitivity analysis introduced by VanderWeele and Ding (13, 14), has the advantage of making minimal assumptions than other techniques. For example, some sensitivity analysis methods considered unmeasured confounders as the only unmeasured variable (15, 16) with the binary level (17, 18) with no interaction between the exposure of interest and unmeasured confounder on the outcome (19, 20). The E-value method, an easy and user-friend method that can be computed even manually, can address these valid criticisms. Therefore, we aimed to evaluate how unmeasured solid confounders may behave to state that the association between IV and COVID-19 hospitalization is not causal.

MATERIALS AND METHODS

COVID-19 Patients

Data on 367 patients aged ≥ 18 who contracted COVID-19 and 103 (28.07 %) received IV were collected at Kerman Afzalipour Hospital and Sirjan University of Medical Sciences, Southeast of Iran. The current research protocol was approved by the ethical committee of Sirjan University of Medical Sciences (IR.SIRUMS.REC.1399.008).

Exposure, potential confounders and outcome

Information about the exposure and potential confounders was extracted from the patients' medical records. IV history and COVID-19 hospitalization were considered the exposure and the outcome, respectively. Age (restricted cubic splines with four knots at the fifth, 35th, 65th, and 95th percentiles), sex, occupation, cigarette smoking, opium use, and pre-existing comorbidities (tabulated in Table 1) were also considered potential confounders.

Statistical analysis

Since the outcome was rare and the exposure was common, we used exposure modeling, i.e. inverse probability weighted (IPW) method, to address the sparse data bias problem. We fitted a logistic regression model to estimate each subject's likelihood of exposure to the IV level given covariates. We used this conditional probability to derive stabilized inverse-probability-of-exposure weights (IPW), known as propensity score. Then we used inverse-probability weighting to create a pseudo-population in which the exposure-outcome association was estimated through a regression model weighted by the IPW. The mean of one for estimated weights is required to show that the model works well. Moreover, to check whether the distribution of confounders was balanced, we used kernel density estimate to visualize the distribution of the weights and propensity score across the exposure level.

We considered CI to draw the magnitude of IV effect on COVID-19 hospitalization and its degree of precision to prevent fallacious interpretation (21). All analyses were performed by Stata version 14 (Stata Corp, College Station, Texas).

Sensitivity analysis

We computed the E-value on the risk ratio (RR) scale for point estimate and the corresponding confidence Interval (CI) lower and upper limits. The E-value explains the minimum strength of unmeasured confounding to completely explain away an exposure-outcome association beyond the measured confounders.

For a better interpretation of the computed E-value, we also calculated E-value for the measured confounders if they had been omitted.

If RR > 1:

E-value (point estimate) = RR + $\sqrt{\boldsymbol{RR} \times (\boldsymbol{RR} - \mathbf{1})}$

E-value (Lower Limit (LL)) = 1 if LL ≤ 1, else LL + $\sqrt{\boldsymbol{LL} \times (\boldsymbol{LL} - \mathbf{1})}$

If RR < 1:

E-value (point estimate) = 1/RR + $\sqrt{\mathbf{1}/\boldsymbol{RR} \times (\mathbf{1}/\boldsymbol{RR} - \mathbf{1})}$

E-value (Upper Limit (UL)) = 1 if UL ≥ 1, else 1/UL + $\sqrt{\mathbf{1}/\boldsymbol{UL} \times (\mathbf{1}/\boldsymbol{UL} - \mathbf{1})}$

RESULTS

The characteristics of patients with COVID-19 (according to their exposure status) are summarized in Table 1. The mean number of comorbidities in exposed and unexposed patients to IV were 1.7 (0.9) and 1.6 (0.9), respectively. Compared with those exposed to IV, the unexposed patients were more likely to be women and use opium, and less likely to be cigarette smokers.

IPW demonstrated 1.12 (95% CI: 0.71 to 1.29) times greater risk in patients exposed to IV than those unexposed. The overlapping plot of weights (Figure 1) shows that the distribution of confounders is completely balanced across the level of exposure after weighting. Moreover, the mean (SD) of IPW was 1.001 (0.21).

Sensitivity analysis demonstrated that the E-value (95% CI) of 1.49 (1.90 to 2.15) was required to shift the RR and the corresponding confidence interval (CI) lower and upper limits toward the null. Furthermore, the most computed E-values for measured confounders (if they had been omitted) were relatively larger than for unmeasured confounders. Therefore the range of the mentioned E-value was from 1.16 to 1.76 for the point estimate, from 1.86 to 2.49 for CI lower limit, and from 1.64 to 2.15 for CI upper limit (Table 2).

Table 1. Characteristics of patients contracted COVID-19 based on expose to influenza vaccination.

	Exposed to influenza vaccination (n=264)		Unexposed to influenza vaccination (n=103)	
	No (%)	Mean (SD)	No (%)	Mean (SD)
Sex (female)	54 (52.4)		145 (54.9)	
Age		43.3 (14.6)		43.8 (16.6)
Occupation (yes)	52 (50.5)		128 (48.5)	
Cigarette smoking (yes)	6 (5.8)		11 (4.1)	
Opium (yes)	6 (5.8)		17 (6.4)	
Number of comorbidities		1.7 (0.9)		1.6 (0.9)

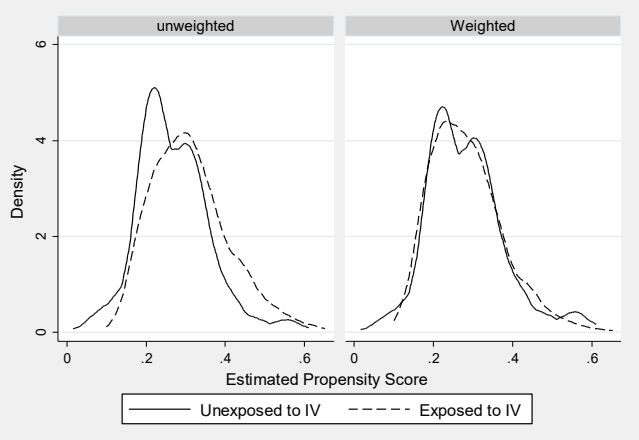

Figure 1. Distribution of confounders by exposure status before and after weighting using IPW

Table 2. E-values for measured confounders if they had been omitted and unmeasured confounders.

	RR E-value	CI lower limit E-value	CI upper limit E-value
Sex	1.62	2.08	2.06
Age	1.16	2.49	1.64
Occupation	1.54	2.13	1.97
Pack-year cigar	1.46	2.17	1.90
Cumulative opium	1.74	1.86	2.15
Number of comorbidities	1.76	2.27	1.92
Unmeasured confounders	**1.49**	**2.15**	**1.90**

DISCUSSION

The current study demonstrated an insignificantly greater risk of COVID-19 hospitalization in IV-exposed patients than the unexposed ones. However, the sensitivity analysis revealed that IV had no positive or negative effect on COVID-19 hospitalization. Sensitivity analysis indicated that the observed negative effect was a weak confounding subject to bias. Through unmeasured confounders such as socioeconomic status, it could fully explain the reported exposure-outcome association.

We observed no positive IV coverage effect, contrary to other studies (1, 3, 9, 11, 12). A study by Feng et al. reported that the vaccination rate of adults (aged 18–59 years) was the lowest, which can be related to the following reasons. First, children (aged six months to 5 years) and adults aged (≥60 years) were designated as a priority group for influenza vaccination (22). Therefore, one may argue that although older people had more underlying diseases and were more likely to be vaccinated, they were also more likely to be dead before inclusion in the study. Consequently, the vaccine efficacy may be influenced by survival bias and age group variations in different studies (23). Furthermore, a survey conducted by Rangi et al. claimed that the IV type could be related to participant characteristics. In this study, compared with a subject who received the tetravalent vaccine, those who received the trivalent vaccine were older with more comorbidities (9). Similar to our research, Rangi et al.(9) observed that the trivalent vaccine increased the hospital admission risk by 12%. However, conversely, they observed a 12% lower risk among those who received the tetravalent vaccine than those who received none. But Fink et al. pointed to the positive effect of the trivalent vaccine (3). Unfortunately, some studies did not clarify the association between the type of the vaccine and COVID-19 outcomes (10-12). The discordance between our results and those of Fink et al. regarding the trivalent vaccine efficacy may stem from the vaccination time. The positive effect of IV against COVID-19 does not last long and may fade away after a short time (24). Since IV is not included in the national vaccination program and is received voluntarily, we had to rely on the subject's memory about when they received the vaccine, which may have distorted our results through recall bias.

The observed protective effect of the vaccine against COVID-19 may have been confounded by differences in health, social behaviors, or socioeconomic status between those who were and those who were not vaccinated. In 2020, a decrease in all viral respiratory infections was seen in several countries, which can be attributed to interventions such as physical distancing, mask-wearing, community education, and lockdowns (25, 26).

In Michigan, the first positive case of COVID-19 was reported on March 10th, 2020, followed by school closures banning large group gatherings. Restrictions were imposed on visiting healthcare and residential facilities on March 13th, and most public places were closed on March 16th. On March 23rd, an official "stay at home" order was issued, and on April 26th, a mask mandate was enforced (27).

Considering the rapid implementation of similar restrictions following the first positive cases which was extended into June 2020, the outcomes of our study may have been influenced by these strict public health interventions. Moreover, differences in adherence to these restrictions between influenza-vaccinated and unvaccinated patients may have biased the observed association. Design and implementation of a prospective study that includes these differences is needed to explore the possible protective effect of the influenza vaccine against COVID-19 susceptibility and the outcomes (27).

Although a positive association between IV and COVID-19 outcomes was observed, the effect size was not strong enough. Furthermore, since all conducted studies were observational, the reported results are subject to bias. In addition, there is a hypothesis that IV may worsen the COVID-19 patients' condition; therefore, it would be valuable to do a sensitivity analysis to analyze how robust the results are. Our sensitivity analysis showed no protective effect of IV against COVID-19 hospitalization. It

is noteworthy that sensitivity analysis using E-value should be interpreted according to the present study. Indeed, the magnitude of the E-value, either large or small, depends on the other risk factor-outcome associations (28). For instance, even an E-value of 3 for a risk ratio of 4 would be small, but this E-value would be significant for a risk ratio of 2. Moreover, other types of biases other than confounding bias, including measurement error and selection bias, may have distorted the causal effects estimates (29).

CONCLUSION

In summary, IPW showed a greater risk of COVID-19 hospitalization among those who received IV. However, sensitivity analysis using the E-value method demonstrated that this association was not necessarily causal, meaning that there was no relationship between receiving IV and COVID-19 hospitalization according to the context of measured confounders. It means that a weaker confounding could fully explain away the observed estimated risk and its corresponding CI lower and upper limit.

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Conflict of interest statement:

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