

The epidemiological and clinical characteristics of the hospital-acquired influenza infections

A systematic review and meta-analysis

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Abstract

Background: The hospital-acquired influenza (HAI) were usually contributed to severe outcomes among the inpatients. Here, we performed a meta-analysis to summarize and quantify the epidemiological and clinical characteristics of HAI.

Methods: We performed a literature search thorough PubMed, Web of Science, Cochrane Library, Embase, Scopus and China National Knowledge Infrastructure (CNKI), and Wanfang databases for observational studies. Random/fix-effects models were used to obtain pooled proportion, odds ratio (OR), and weighted mean difference (WMD).

Results: A total of 14 studies involving 1483 HAI and 71849 non-hospital-acquired influenza infections (NHA) cases were included. The proportion of the HAI among the influenza cases was 11.38% (95% confidence interval [CI]: 5.19%–19.55%) and it was increased after 2012 (6.15% vs 12.72%). The HAI cases were significantly older (WMD=9.51, 95% CI: 0.04–18.98) and the patients with chronic medical diseases were at increased risk of HAI (OR=1.85, 95% CI: 1.57–2.19). Among them, metabolic disorders (OR=8.10, 95% CI: 2.46–26.64) ranked the highest danger, followed by malignancy (OR=3.18, 95% CI: 2.12–4.76), any chronic diseases (OR=2.81, 95% CI: 1.08–9.31), immunosuppression (OR=2.13, 95% CI: 1.25–3.64), renal diseases (OR=1.72, 95% CI: 1.40–2.10), heart diseases (OR=1.52, 95% CI: 1.03–1.44), and diabetes (OR=1.22, 95% CI: 1.03–1.44). The HAI cases were more likely to experience longer hospital stay (WMD=10.23, 95% CI: 4.60–15.85) and longer intensive care unit (ICU) stay (WMD=2.99, 95% CI: 1.50–4.48). In the outcomes within 30 days, those population was still more likely to receive hospitalization (OR=6.55, 95% CI: 5.19–8.27), death in hospital (OR=1.99, 95% CI: 1.65–2.40) but less likely to discharged (OR=0.20, 95% CI: 0.16–0.24).

Conclusion: The proportion of the HAI among the influenza cases was relatively high. Reinforcement of the surveillance systems and vaccination of the high-risk patients and their contacts are necessary for the HAI control.

Abbreviations: 95% CI = 95% confidence interval, CNKI = China National Knowledge Infrastructure, HAI = hospital-acquired influenza, IARH = influenza-associated respiratory hospitalizations, IQR = interquartile range, NHA = non-hospital-acquired influenza infections, OR = odds ratio, R0 = average basic reproductive number, WHO = World Health Organization, WMD = weighted mean difference.

Keywords: clinical characteristics, hospital-acquired influenza, meta-analysis, risk factors

1. Introduction

Human influenza is a contagious acute respiratory illness caused by influenza A and B virus.^[1] About 5% to 10% adults and 20%

to 30% children, by estimation, got infections annually, which would cause 290,000 to 650,000 deaths per year worldwide.^[2] The hospital-acquired influenza (HAI) cases usually occurred at

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the annual peak of community influenza activity and the influenza cases, healthcare workers, and visitors were recognized to be the most common sources.^[3] The hospitalized patients were vulnerable to influenza virus infections and at high risk of severe outcomes and mortality and the frequently outbreaks have been reported in intensive care units, geriatric, pediatrics, and hematological units.^[4,5] The attack rate of nosocomial influenza outbreaks was at a range of 12% to 60%.^[6] Once the HAI occurred, the Intra-ICU mortality could be as high as 30% to 40%.^[7] In 2004 to 2017, the HAI was the top causes of public health emergencies within hospitals in China.^[8]

Nowadays, the incidence of HAI is deemed to be underestimated.^[9] The prevention and control of the HAI is of great importance for risk management in hospital to ensure patient safety and limit the costs of healthcare organizations. Several studies have reported the clinical characteristic of the HAI.^[10–12] However, the features of HAI present low inconsistency and no systematic summarization, due to the limited samples and available data. For example, pediatric nosocomial H1N1 was reported generally mild in clinical outcomes and rarely needed aggressive medical previously.^[13,14] However, it showed the reverse outcome in the hospital-acquired H1N1 surveillance in UK.^[15] Hence, we pooled the published data to clarify what definite proportion of HAI among the influenza cases and to identify the epidemiological and clinical characteristics of HAI, hoping to inform the development of the specific control measures in the future.

2. Methods

2.1. Search strategy

A comprehensive systematic literature search on the studies published from January 01, 1928 to August 23, 2020 was conducted was conducted through the databases including PubMed, Web of Science, Cochrane Library, Embase, Scopus, and China National Knowledge Infrastructure (CNKI) and Wangfang. The search terms were as follows: influenza, flu, nosocomial, hospital infection, hospital-acquired, and related-terms. The details of search strategy were showed in the Supplementary Table 1, <http://links.lww.com/MD/F915>. This study did not require ethical approval since all analyses were based on previously published studies.

2.2. Inclusion and exclusion criteria

The inclusion criteria were: hospital-acquired influenza was defined as onset of influenza-related symptoms >48 hours after an admission to the hospital. Both HAI and non-hospital-acquired influenza infections (NHAI) cases were confirmed by Reverse Transcription-Polymerase Chain Reaction (RT-PCR). The studies included sufficient data to describe the demographical and clinical characteristics of both HAI and NHAI cases. The exclusion criteria were: studies only with HAI cases; the duplicated publications data; case reports, abstract, review, and the studies missing the key data or without original data.

2.3. Data extraction and quality assessment

The following data were extracted from the studies including basic information of the studies (e.g., article titles, first author), demographic data (e.g., sex, age), the chronic medical diseases

(e.g., metabolic disorders, malignancy), influenza vaccination status, the proportions of influenza A and B virus, treatment (whether treated with antivirals or antibiotics), time intervals (e.g., days from symptom onset to treatment, length of hospital stay), the rate of ICU admission, 30 days results (still hospitalized, discharged, or death in hospital). According to the Agency for Healthcare Research and Quality,^[16] the scale that contains 11 items was used to assess the quality of each included study. The studies were defined as low (0–3), moderate (4–7), and high-quality (8–11), respectively.

2.4. Statistical analysis

The proportion of the HAI was pooled estimation and their 95% confidence interval (95% CI) was reported. The continuous variables including series of time intervals and age were converted to mean and standard deviation if described by median and interquartile range (IQR)/range and then weighted mean difference and its 95% was calculated.^[17] The odds ratio and its 95% CI was calculated among categorical variables to evaluate the risk association with HAI. The heterogeneity among the meta-analysis was evaluated by I^2 and the random-effects model was chosen when $I^2 > 50\%$.^[18] The potential publication bias was appraised by funnel plot.^[19] Additionally, sensitivity analysis was conducted to evaluate the impact of each study on the overall pooled estimate. R version 3.2.3. was used to perform the data clearing and analyses.

3. Results

3.1. Search results

A total of 9049 studies were retrieved. After duplicates removed, the titles and abstracts of 5132 literature were screened and then 130 full-text articles were performed the detailed assessment. Among them, 43 lack clinical characteristics data, 15 studies with only HAI cases, 51 lack key data available for the both HAI and NHAI cases, 7 duplicate publications data. Finally, 14 studies containing 1529 HAI and 71941 NHAI influenza cases were included in our study (Fig. 1). The details were showed in Table 1.

3.2. The proportion of the hospital-acquired influenza among the influenza cases

The proportion of the hospital-acquired influenza among the influenza cases was 11.38% (95% CI: 5.19%–19.55%). Compared with the before 2012, the proportion of the HAI increased after 2012, from 6.15% (95% CI: 0–21.80%) to 12.72% (95% CI: 11.41–14.08%) (Fig. 2), (Supplementary Figure 1, <http://links.lww.com/MD/F907>).

3.3. The age and chronic medical diseases association with hospital-acquired influenza

Compared with the NHAI cases, the HAI cases were significantly older (WMD=9.51 year, 95% CI: 0.04–18.98), (Fig. 3A), (Supplementary Figure 2, <http://links.lww.com/MD/F908>). The chronic medical diseases were associated with HAI (OR=1.85, 95% CI: 1.57–2.19). Among them, metabolic disorders (OR=8.10, 95% CI: 2.46–26.64) showed extremely dangerous and followed by malignancy (OR=3.18, 95% CI: 2.12–4.76), any chronic diseases (OR=2.81, 95% CI: 1.08–9.31), immunosup-

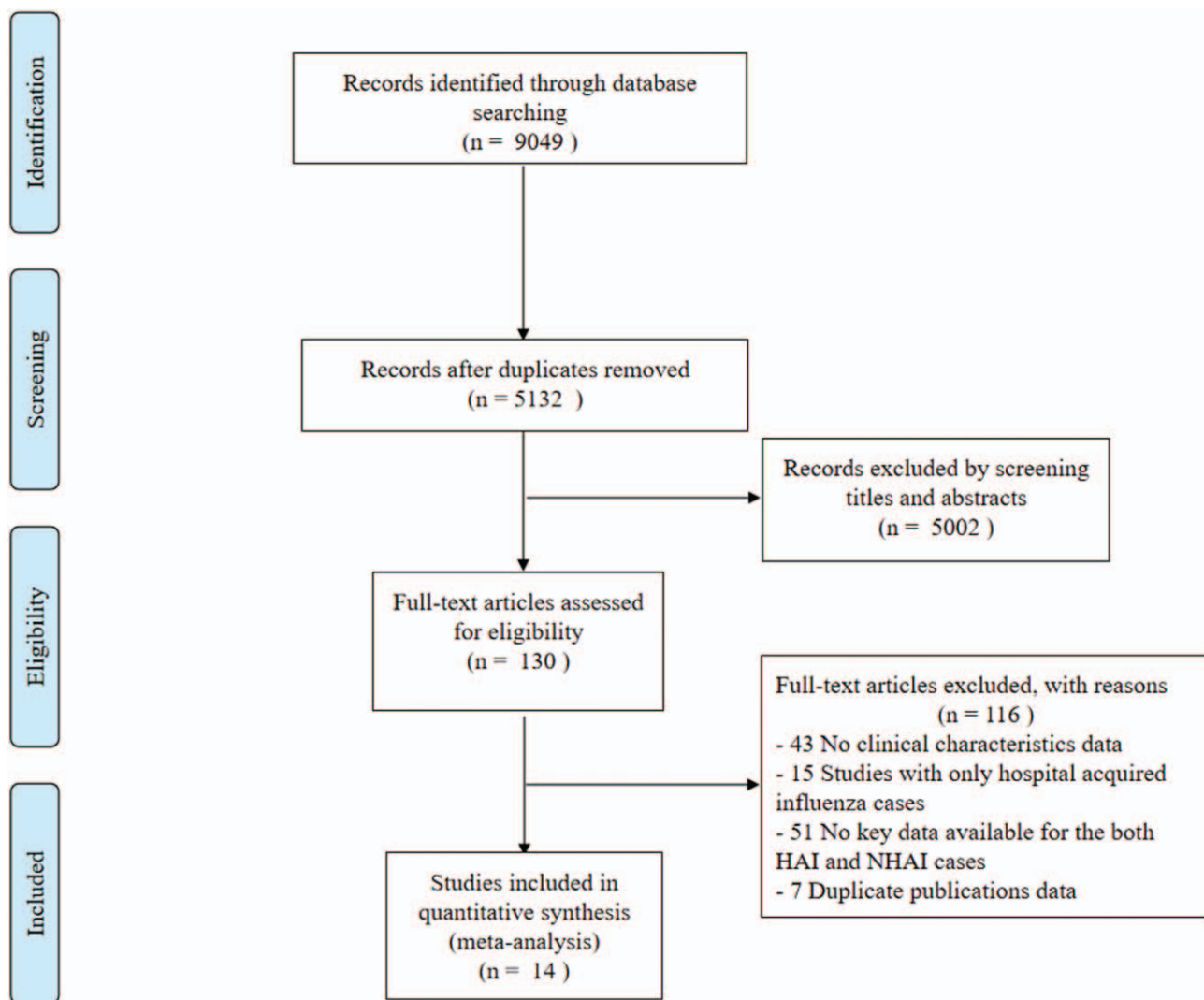


Figure 1. Flow diagram of the study selection process for this meta-analysis.

pression (OR=2.13, 95% CI: 1.25–3.64), renal diseases (OR=1.72, 95% CI: 1.40–2.10), heart diseases (OR=1.52, 95% CI: 1.03–1.44), and diabetes (OR=1.22, 95% CI: 1.03–1.44) (Fig. 3B), (Supplementary Figure 3, <http://links.lww.com/MD/F909>).

3.4. The clinical characteristics and outcomes of hospital-acquired influenza

There were no statistical differences between the influenza vaccinations status. The prevalence of influenza A and B virus, whether received antivirals and antibiotics, the rate of ICU admission and days from symptom onset to diagnose between the HAI and NHAI (Fig. 4A, B), (Supplementary Figure 4, <http://links.lww.com/MD/F910>, <http://links.lww.com/MD/F911>). However, the HAI cases were early to be treated (WMD=−2.14 days, 95% CI: −3.2 to −1.08) and received antivirals within 48 hours from symptom onset (OR=4.26, 95% CI: 1.82–9.96). The HAI cases were more likely to experience longer hospital stay (WMD=10.23 days, 95% CI: 4.60–15.85) and longer ICU stay (WMD=2.99 days, 95% CI: 1.50–4.48), (Fig. 4B). In the outcomes of 30

days, the HAI were more likely to be hospitalized (OR=6.55, 95% CI: 5.19–8.27), died in hospital (OR=1.99, 95% CI: 1.65–2.40), and less likely to be discharged (OR=0.20, 95% CI: 0.16–0.24) (Fig. 4C), (Supplementary Figure 6, <http://links.lww.com/MD/F912>).

3.5. Publication bias and sensitive analysis

The shapes of the funnel plot were symmetry which suggested no suspected publication bias (Supplementary Figure 7, <http://links.lww.com/MD/F913>). The results of sensitive analysis showed that the meta-analysis was stable which no single study altered the pooled proportion estimates (Supplementary Figure 8, <http://links.lww.com/MD/F914>).

4. Discussion

Previously, the nosocomial infections surveillance systems more mainly focused on the nosocomial bacterial infections, while nosocomial viral infections were less likely to be reported, due to historical attention to bacterial infection, difficulties of viral

Table 1
The characteristics of studies included in this meta-analysis.

No	Title	First author	Year	Journal name	Study period	Region	Sample size	Study design	Study quality
1 ^[20]	Hospital-acquired influenza in an Australian sentinel surveillance system	Nenad Macesic	2013	Med J Aust	2010–2011	Australian	598	Cross-sectional	6
2 ^[10]	Hospital-acquired influenza in an Australian tertiary Centre 2017: a surveillance based study	Nikita Parkash	2019	BMC Pulmonary Medicine	2017	Australian	292	Cross-sectional	6
3 ^[21]	Healthcare-Associated Influenza in Canadian Hospitals from 2006 to 2012	Geoffrey Taylor	2014	Infection Control And Hospital Epidemiology	2006–2012	Canada	3299	Cross-sectional	6
4 ^[22]	Risk factors and clinical characteristics of patients with nosocomial influenza A infection	Pauline Naudion	2019	Journal of Medical Virology	2016/12–2017/02	France	208	Cross-sectional	7
5 ^[23]	Incidence and characteristics of nosocomial influenza in a country with low vaccine coverage	D. Luque-Paz	2020	Journal of Hospital Infection	2017/12–2018/04	France	860	Cross-sectional	6
6 ^[24]	Impact of nosocomial transmission of influenza virus in an acute hospital	José L. Mendoza-García	2018	Rev Esp Salud Pública	2016–2017	Spain	286	Cross-sectional	5
7 ^[11]	Nosocomial vs community-acquired pandemic influenza A (H1N1) 2009: a nested cases-control study	G. Khandaker	2012	Journal of Hospital Infection	2009/06–2009/09	Australia	506	Cases-control	7
8 ^[25]	Characterisation of nosocomial and community-acquired influenza in a large university hospital during two consecutive influenza seasons	Daniela Huzly	2015	Journal of Clinical Virology	2013/01–2014/04	Germany	218	Cross-sectional	7
9 ^[26]	Characteristics and management of patients with influenza in a German hospital during the 2014/2015 influenza season	Stefan Hagel	2016	Infection	2014/2015	Germany	197	Cross-sectional	7
10 ^[12]	Hospital-acquired influenza infections detected by a surveillance system over six seasons, from 2010/2011 to 2015/2016	P. Godoy	2020	BMC Infectious Diseases	2010–2016	Spain	1722	Case-case	8
11 ^[27]	Can influenza vaccination coverage among healthcare workers influence the risk of nosocomial influenza-like illness in hospitalized patients?	E. Amodio	2014	Journal of Hospital Infection	2005–2012	Italy	62343	Cross-sectional	6
12 ^[7]	Characteristics of patients with hospital-acquired influenza A (H1N1)pdm09 virus admitted to the intensive care unit	F. A'lvarez-Lerma	2017	Journal of Hospital Infection	2009–2015	Spain	2421	Cross-sectional	7
13 ^[28]	Risk Factors for Healthcare-Associated, Laboratory-Confirmed Influenza in Hospitalized Pediatric Patients: A Case-Control Study	Kateri H. Leckerman	2010	Infection control and hospital epidemiology	2000–2004	United State	138	Case-control	8
14 ^[29]	Intermittent occurrence of health care-onset influenza cases in a tertiary care facility during the 2017–2018 flu season	Bischoff W	2020	American Journal of Infection Control	2017–2018	United State	382	Case-control	7

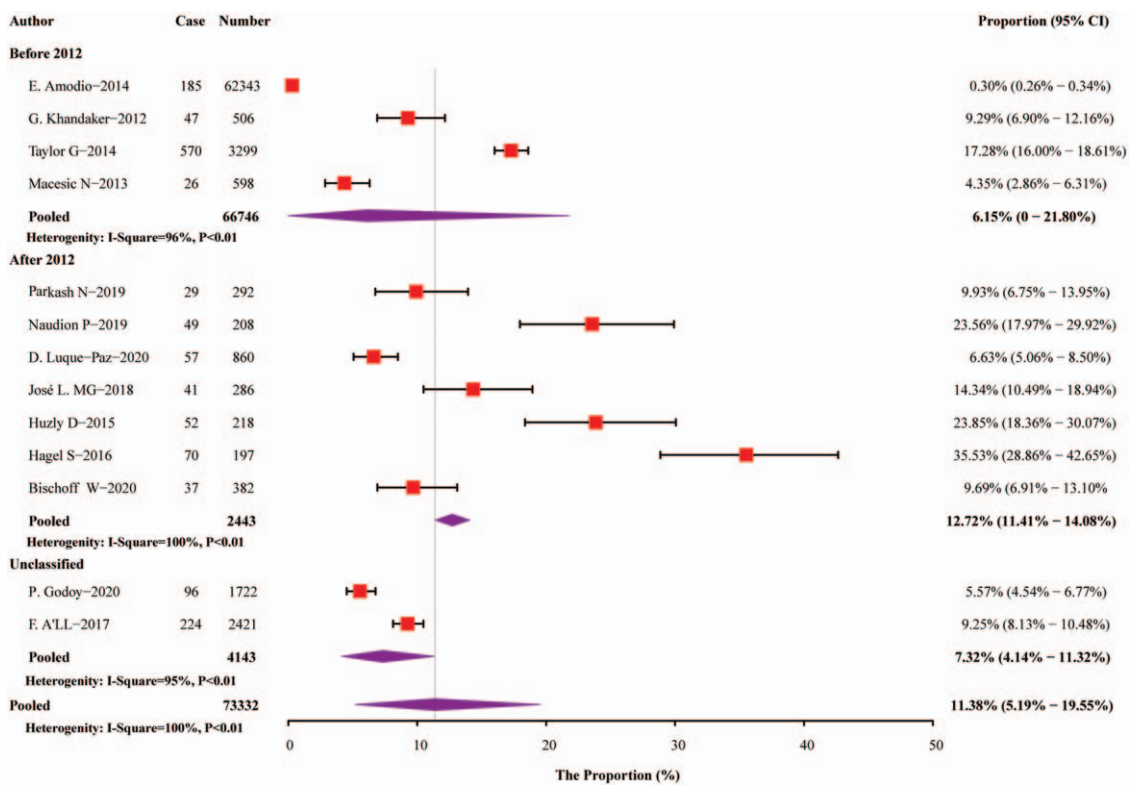


Figure 2. The proportion of the HAI individuals among the influenza case. HAI=hospital-acquired influenza.

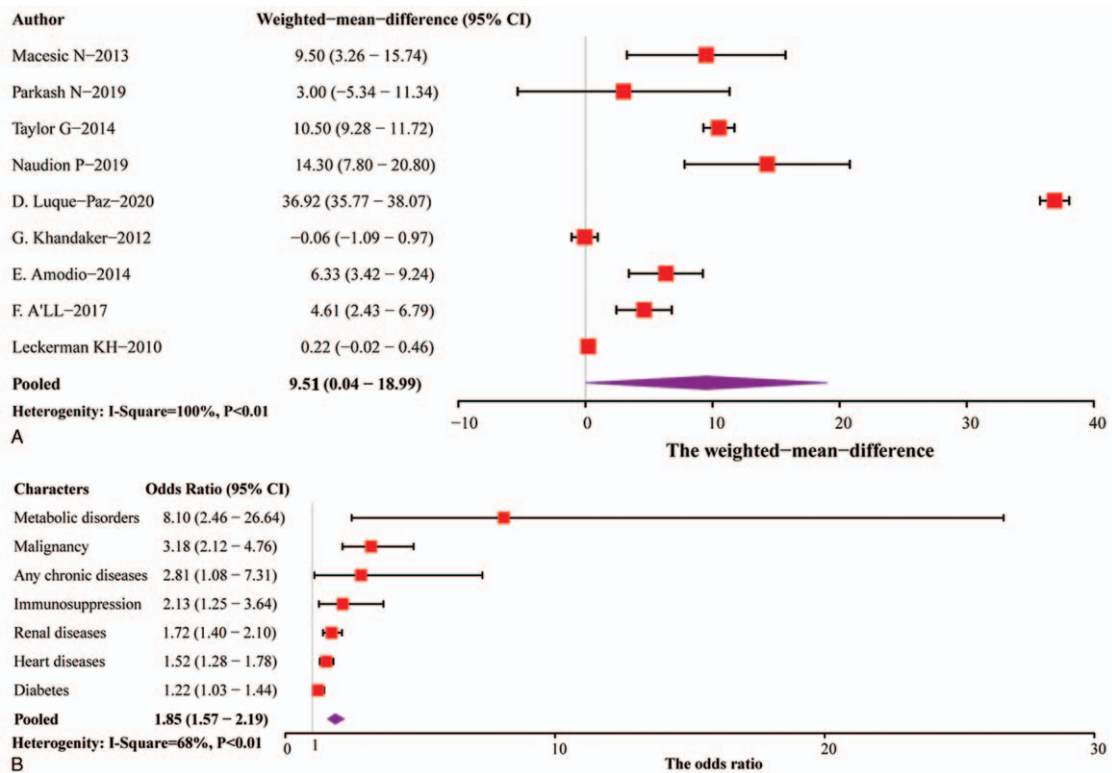


Figure 3. The estimated WMD and pooled OR on age and chronic medical diseases between HAI and NHAI. (A) The estimated WMD on age between HAI and NHAI. (B) The pooled OR between HAI and NHAI. HAI = hospital-acquired influenza, NHAI = non-hospital-acquired influenza infections, OR = odds ratio, WMD = weighted mean difference.

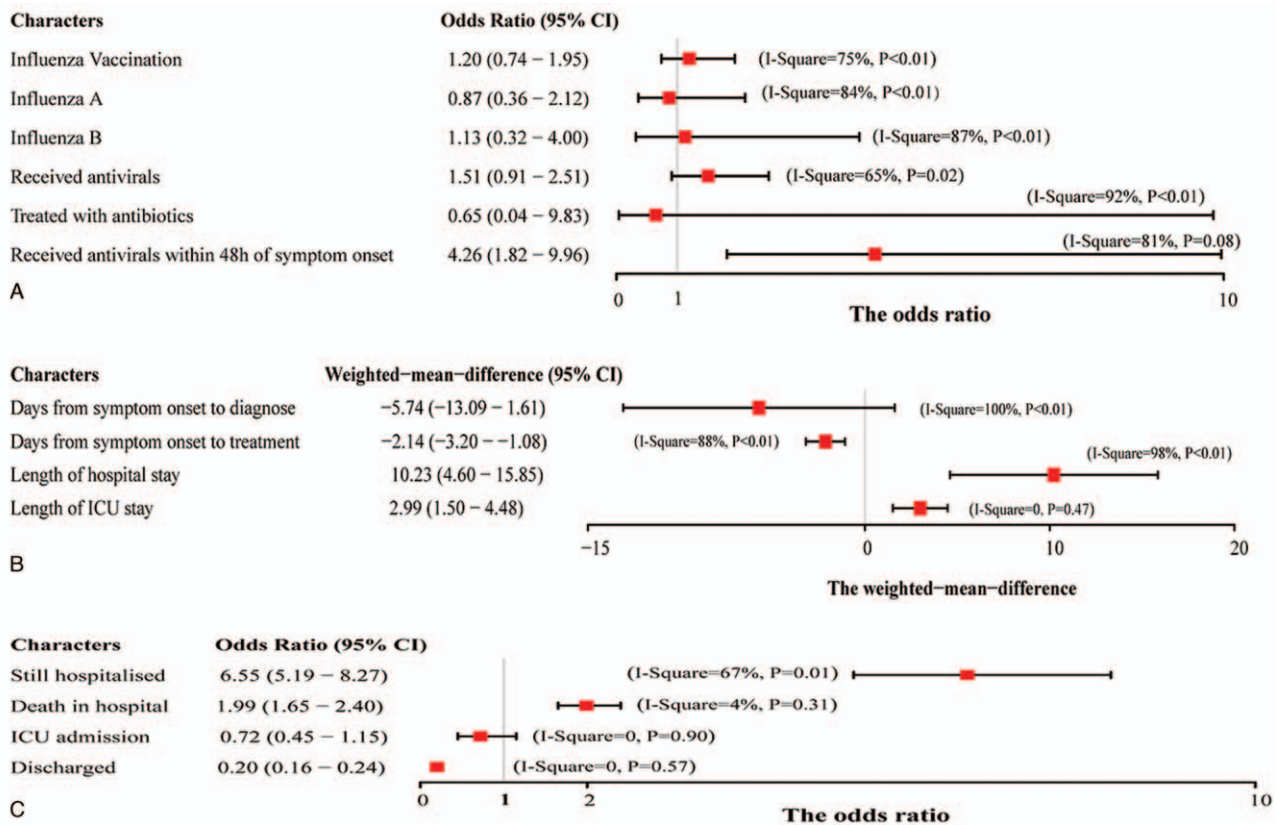


Figure 4. The pooled OR estimated WMD on treatments, time intervals, and outcomes between HAI and NHAI. (A) The pooled OR on treatment between HAI and NHAI. (B) The estimated WMD on time interval between HAI and NHAI. (C) The pooled OR on outcomes between HAI and NHAI. HAI = hospital-acquired influenza, NHAI = non-hospital-acquired influenza infections, OR = odds ratio, WMD = weighted mean difference.

diagnose, and limited effectiveness of antiviral drugs.^[9,30] However, the nosocomial viral infections can usually lead to severe outcomes and cause heavy economic burden on patients, families, and healthcare systems.^[31] Emergence of multi-drug resistant organisms were also found.^[5] The average basic reproductive number (R0) of influenza was from 1 to 2.^[32] Exposure to influenza patients is considered as a highly risk factor for hospital-acquired influenza.^[33] In the Americas, the average annual number of influenza-associated respiratory hospitalizations (IARH) was estimated to be 772,000^[34] and it was had 28,516 in a mean season in the United Kingdom.^[35] As heavy burden of IARH which served as a large number of potential sources of infection of nosocomial influenza, it would remain constantly challenging in our healthcare setting.

The proportion of the HAI among the influenza cases showed highly geographic differences, from 0.3% in Italy to 35.53% in Germany.^[26,27] A study was excluded when pooling the proportion of the HAI among the influenza cases due to case-control design (Leckerman et al^[28]). Overall, it was estimated 11.53% in our study. We noticed that the proportion of the HAI increased after 2012. During the 2009 influenza H1N1 pandemic, the rate of nosocomial infections was highly raised and several nosocomial influenza outbreak was found.^[14,36] Since then, the advances in the surveillance capacity of nosocomial infections and development of diagnostic ability of pathogens would improve the detection ability of nosocomial viral infections.^[37,38] Noteworthy, no standardized definition of

HAI was available and the most common time interval was between admission and onset ranges from 24 to 72 hours.^[10,24] This may also have impacts on the surveillance results of HIA. Due to the poor health status and chronic medical conditions, the older suffered higher risk of getting the influenza infections in-hospital. This was also observed in many studies.^[20,23] The metabolic disorders could impair host defence and immune cell activity and then increased likelihood of infections.^[39] It could reduced immunogenicity in response to influenza vaccination.^[40] Immunosuppression population includes persons with solid organ and hematopoietic stem cell transplants, malignancies, and autoimmune conditions.^[41] Such people were proven to be at high risk of reinfections in the hospitals.^[42] At the same time, they were also recommended by World Health Organization (WHO) as the prioritized group to be vaccinated influenza vaccines because they are more likely to develop the severe complications and outcomes.^[43] It indicates that people who usually contacts with those population particularly healthcare workers should receive the influenza vaccines to avoid being a source of transmitting influenza virus to their patients and coworkers.^[44] And a previous study showed that higher influenza vaccination coverage among healthcare workers could significantly reduce incident rate of HIA among patients.^[45]

Compared with NHIA, the patients with HIA were found early to receive treatment quickly as well as antivirals within 48 hours from symptom onset. However, it was still enough, almost 40% of patients could received antivirals timely^[10,12] and the days

from symptom onset to diagnosis was no statistical differences between the HIA and NHIA. This may reflect rapid influenza diagnostic tests should further improve which was helpful to implement quickly of control measures. The patients with HIA were experienced longer hospital and ICU stay and high risk to death in hospital. In a pediatric outbreak, additional cost of \$7545 per case by prolonged of 8 days hospitalization.^[46] And it puts heavy burden on the medical resource due to requiring more health costs, staff care, beds in wards and ICU, and closure of wards was caused by nosocomial influenza/parainfluenza outbreak.^[47] A survey based on 221 health-care institutions revealed that 35% of hospitals faced staff shortages, 28% faced bed shortages, and 43% faced intensive care unit bed shortages during the peak influenza epidemic.^[48] Nowadays, our world is attacking by COVID-19. The cases co-infected of SARS-CoV-2 and influenza virus were found in many studies.^[49,50] It is highly concerned that a second pandemic wave of COVID-19 will starting in this fall/winter which may overlap with seasonal influenza. In this era, the prevention and control of HIA was necessary to avoid medical resources wasting and reduce the likelihood for cross-infection in the hospital.

Our study has several limitations. Firstly, the high statistic heterogeneity was found, this may related to the sample sizes, study populations, and study periods. Secondly, all included studies were from high-income countries. It is unclear whether these factors associated with HAI vary among epidemics of different country. More studies from different countries are needed in the future. Thirdly, the information associated with HAI were insufficient in several studies which may lead to some biases when pooled the data.

5. Conclusions

In our study, the proportion of the HAI among the influenza cases was estimated to be 11.38%, the older of age and chronic medical diseases including metabolic disorders, malignancy and immunosuppression, renal diseases, heart disease, and diabetes were main risk factors for the HAI. Compared with the NHAI, the patients with HAI were treated earlier and received antivirals within 48 hours from symptom onset. Such population experienced longer periods of hospital and ICU stay and poor 30 days outcomes including more likely to still hospitalized, less to discharge, and high risk of death in hospital. In order to better prevent and control HAI, it is important to continuously enhance and improve of surveillance systems of HAI and develop of more efficiently rapid diagnostic reagents to implementation of control measures timely. The influenza vaccination among the high-risk patients and their contacts, especially healthcare worker is necessary.

Author contributions

Conceptualization: Yi Li, Lan-Lan Wang, Li-Li Xie, Wei-Lian Hou, Xiao-Yi Liu, Shi Yin.

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