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SYSTEMATIC REVIEW

Prediction models for prognosis of influenza: a systematic review and critical appraisal

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Abstract

The influenza epidemic has become an important public health issue throughout the world. Early recognition of potentially terrible outcomes is important in the emergency department (ED). Efficient prognosis of the disease is conducive to reducing the financial burden and providing appropriate care for patients. Prediction models containing several features to estimate the risk of patients with confirmed infection could help clinicians give appropriate treatment when health care resources are limited. We conducted a literature review of studies about influenza published until June 2021 and updated the literature during the creation process. We researched PubMed, Web of Science, and Google Scholar databases to collect articles in English relevant to influenza between Jan 1, 1900, and Dec 30, 2020. The terms used for the search were "influenza", "diagnostic", "prognostic", "prediction", "score", "artificial intelligence", and so on. If the study involved animals, children, pregnant women or the study type was pragmatic and explanatory clinical trial, guideline, protocol, letter, a case report was also excluded. The GRACE checklist in our study was used to assess the 34 studies for quality. Thirty-four articles were included in the review, and relevant data were extracted from the risk prognosis model. Cardiovascular disease and central nervous symptoms play an important role in prognostic models of influenza. In addition, some commonly used scoring systems can also play a certain role in evaluation. This systematic review compared different types of models for predicting the prognosis of influenza infection, informing us of risk factors for the predictive model in predicting the prognosis of influenza in the early stage. The articles were limited to retrospective observational studies, sample size, time limitation, incomplete data, imbalanced prognosis treatment, and so on.

Keywords

Prediction models; Prognosis; Influenza; Review; Critical appraisal

1. Introduction

Community influenza activity has long been a serious threat to global public health [1–5]. During seasonal epidemics, the number of severe cases registered worldwide is 3 to 5 million, and the number of lethal cases is 250,000–500,000 [6, 7]. The prognosis of influenza patients ranges from asymptomatic infection to severe pneumonia and even acute respiratory distress syndrome (ARDS) and multiple organ dysfunction syndrome [1, 8–10]. Influenza progresses rapidly, usually leading to morbidity and mortality within days [11, 12]. In addition, influenza will increase the mortality rate of elderly patients or patients with underlying diseases [5, 13–18]. The evolution and reassortment of influenza viruses are the main power that would generate novel strains, against which the humans have no or little immunity [19, 20].

In the emergency department, it is important to identify flu patients with poor prognosis early and to be alert and pay attention to them [11, 21]. To reduce the burden on the health care system and provide patients with the best care, it is necessary to effectively predict the prognosis of the disease and carry out early intervention [1, 22, 23]. In clinical medical research, a large number of predictive models that combine multiple variables or characteristics have been developed to estimate the risk of people being infected or the risk of adverse consequences after infection, which can help medical staff treat patients when they allocate limited medical resources [24–28]. Models ranging from regressive scoring systems to advanced machine learning have been proposed and released in response to calls for rapid public sharing of relevant influenza research results to inform public health responses and help save lives [3, 9, 29–31]. However, the models developed using machine learning are mostly basic research on influenza virus infection, and do not include clinical evaluation content [32].

To date, there has not been a systematic review or meta-analysis of the prognostic model of influenza infection. We

aim to systematically review and critically evaluate the currently available influenza prognostic prediction models.

2. Materials and methods

This study evaluates the predictive power of prognostic models of influenza patients in different studies.

2.1 Data sources and search strategy

First, the databases PubMed, Web of Science and Google Scholar were searched to collect and identify articles in English that were relevant to influenza between Jan 1, 1900, and Dec 30, 2020. Relevant searches were also carried out during writing. The key terms used for the search were "influenza", "human influenzas", "Flu", "Grippe", "diagnostic", "prognostic", "prediction", "prediction model", "regression", "score", "artificial intelligence", "algorithm", "deep learning", "machine learning", "CURB-65", and "PSI". We made various combinations of these words. We also included documents in the references that met the requirements for further inspection.

2.2 Study selection and data extraction

We included all English language full text articles that described retrospective and prospective observational studies, and randomized controlled trials. Inclusion criteria for studies were based on existing standards for diagnosis of influenza from research. If infection is suspected, a nasopharyngeal tract sample for conventional influenza RT-PCR should always be obtained. Antigen testing and direct or indirect antibody staining tests should only be used in settings lacking the more sensitive molecular assays. Participants included in the articles should be diagnosed with the infection of at least one type of influenza. The study should enroll adult patients ($\geq$16 years) with in-hospital confirmed influenza. We chose the evaluated mortality as an outcome of interest (in-hospital, 30-day, or 90-day mortality) in our study. We did not include studies involving animals, children, or pregnant women, or those not written in English. Pragmatic and explanatory clinical trials, guidelines, protocols, letters, case reports, or case series were also excluded.

First, the titles and abstracts we drew were screened and selected by two authors (YS and YWZ). To ensure that information was accurate and determine final eligibility, all reviewers (YS, YWZ, and SZ) screened full texts of likely articles. The authors (YS and YWZ) further selected articles that were relevant to the prognosis of influenza. Meanwhile, we (YS, YWZ, and SZ) identified the risk factors related to influenza infection. We all worked independently, and team members all contributed to review and data extraction to avoid discrepancies and questions, reaching a consensus. If there was any disagreement, the third one would join in and give a decision.

We imported all searched articles into the literature management software Endnote 9.2 (Thomson Reuters, New York, NY, USA) and excluded all duplicate articles by comparing the title, authors, publication year, and name of the journal. Once we determined the articles, data was extracted and transferred to standardized form by one team member using Microsoft Office Excel and Word 2016 (Microsoft, Redmond, WA, USA), and the other team member verified the accuracy. The form was discussed and designed by all reviewers. The form-filling criteria were also determined by three creators.

This systematic review has applied and passed the international platform of registered systematic review and meta-analysis protocols (INPLASY 202120047) on February 16, 2021 (doi:10.37766/inplasy2021.2.0047), hoping that the whole process will be scientific and concrete.

2.3 Quality assessment

The process of study selection and data extraction in whole is presented in the flow chart following the PRISMA principle. We selected the GRACE (Good Research for Comparative Effectiveness) guidelines for rating the quality of studies [33]. Quality ratings were assigned by two separate raters (YS and YWZ) for each publication using the GRACE checklist, which was published by the Academy of Managed Care Pharmacy. It comprises 11 items, split into data and methods. At the same time, we used the GRADE as an auxiliary evaluation method, which is endorsed by the World Health Organization. the overall quality of evidence was graded as high, moderate, low, or very low, according to the Grading of Recommendations Assessment, Development and Evaluation guidelines. Both tools showed consistency. Any conflict was resolved by consensus. Every team member participated in improvement of the GRACE checklist.

3. Results

3.1 Study search result and selection

The searches in PubMed, Medline, Web of Science and Google Scholar initially resulted in 4672 potential eligible articles. We also collected 122 articles through references and other related methods, initially retrieving 4778 articles after using the document manager EndNote to remove the same ones. After reading the titles and abstracts, 268 remained for further full-text screening. Finally, 28 (10%) of 268 met the inclusion criteria for the review, and 240 (90%) were excluded because of the following reasons: 8 (3%) for no outcome, 17 (7%) for pregnancy, 13 (6%) for children, 25 (10%) for the study type doesn't match, and 177 (74%) for other reason that didn't meet the inclusion criteria. We once again retrieved 6 additional articles related by browsing the full text and related information (Fig. 1) [34–39].

Carefully reading the original text, we extracted the year of article, types of article, geographic region, data collection, number of centers and patients, average age, and final outcome. We collected the overall evaluation indicator AUCs for the model provided by each article (Appendix Table 3, Ref. [1, 3, 6, 9, 11, 24–26, 28–30, 34–56]).

Eighteen (53%) items focused on 2009 and 2010 [26, 29, 35, 37, 38, 40–50]. Only 4 (12%) collected patient data earlier than 2009 [24, 34, 51, 52]. Twelve (35%) articles belonged to a multicenter study based on the prevalence of influenza [26, 34, 36, 40–43, 45–48, 51, 53]. However, only 5 (15%) were prospective studies [6, 36, 41, 43, 47, 50, 54].

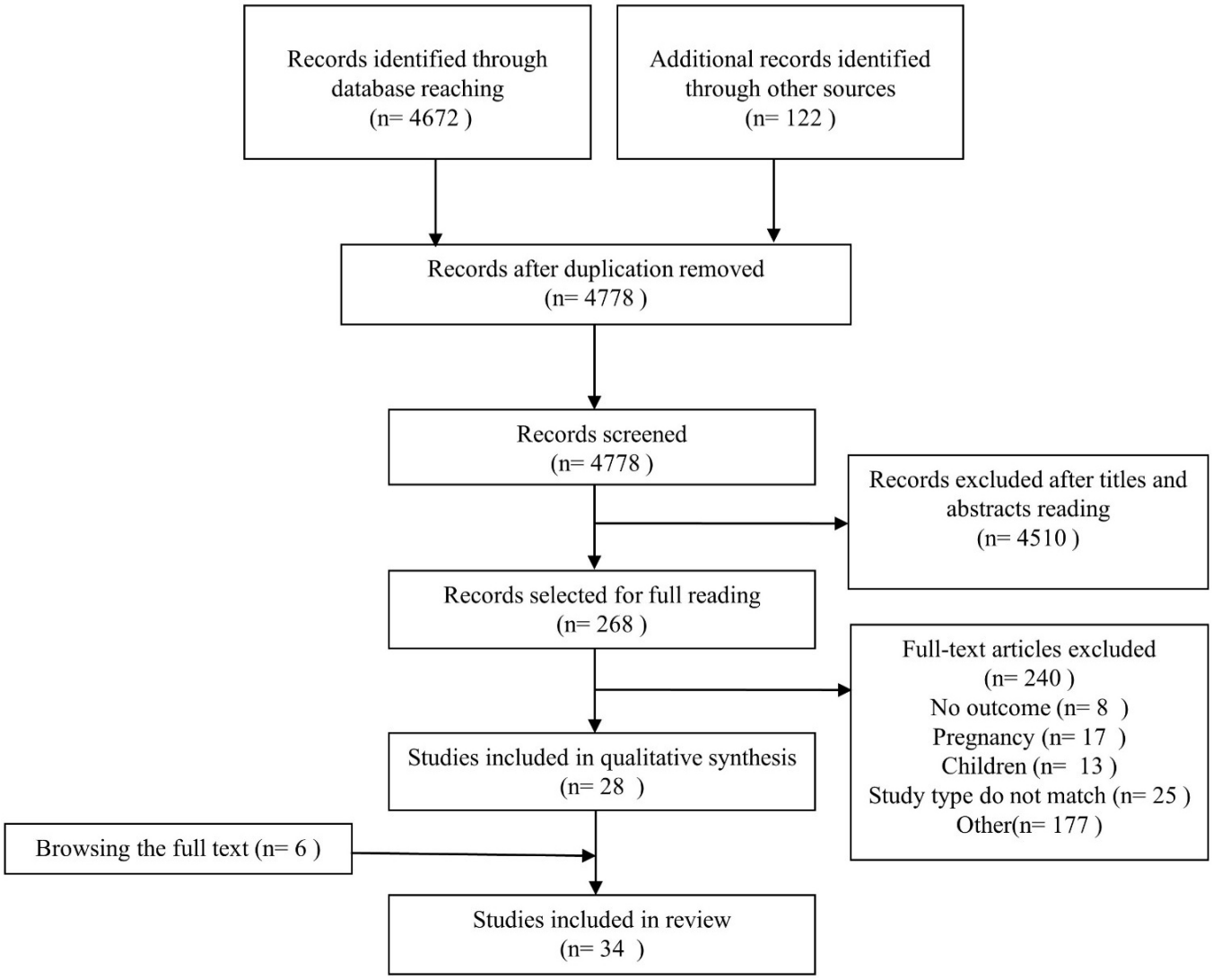

FIGURE 1. Flow diagram of study selection process.

3.2 The risk factors

For different models included in the studies, we reviewed the risk factors related to the prognosis and outcome of influenza. Then, we summarized different risk factors and displayed them in the form of a table. A total of 42 relevant risk factors were calculated in 34 articles, and each factor had a different proportion (Table 1).

In regard to population and medical history, age and cardiovascular disease seem to have a relatively large impact on the prognosis of influenza. Central nervous system (CNS) symptoms play an important role in clinical manifestations. Blood pressure, respiratory rate, and dehydration of the body state have equal shares and cannot be ignored. In laboratory tests, inflammation, abnormal liver function, and a reduction in the number of various types of cells all affect the outcome of patients. In particular, nosocomial infections might be one of the risk factors that we should consider in the future. In addition, it is also necessary to consider whether upper respiratory tract and other viral infections would affect the outcome of the patient. Many types of viral infections can cause thrombocytopenia [57]. The pathogenesis includes the formation of immune complexes, changing the structure of platelet membrane glycoproteins, activating the complement system, forming nuclear virus inclusion bodies and enhancing the activity of the mononuclear-macrophage system. Thrombocytopenia is also one of the prognostic indicators of influenza virus infection according to our review. If there are obvious lung imaging abnormalities on imaging, it means that there has been an organic disease, and the virus has affected the respiratory system. In approximately 4 times the models mentioned, pneumonia imaging and abnormal CR or CT should be risk factors for influenza infection. Many common severe respiratory disease or self-created scoring systems showed good guidance, and the PaO_2/FiO_2 ratio, which shows the oxygenation of blood gas in the lungs, performed the best. Common interventions such as oral antiviral drugs, even if taking statin drugs, could improve the poor prognosis of patients.

3.3 Quality assessment

The GRACE checklist in our study was used to assess the 16 studies for quality (Table 2). The 11-item checklist assesses data attributes and methods (Items D1–6 and M1–5, respectively) [33]. Items were classified as sufficient or insufficient

TABLE 1. The risk factors for the prognosis of influenza.

Category	Content	Times	Percentage (Times) [a]	Total times
Population data and medical history	Age	5	0.06	25
	Gender	1	0.01	
	Smoking	1	0.01	
	BMI	1	0.01	
	Cardiovascular disease	7	0.09	
	Atrial fibrillation	1	0.01	
	Kidney disease	3	0.04	
	Malignant disease	3	0.04	
	Diabetes mellitus	1	0.01	
	Metabolic syndrome	1	0.01	
	Number of comorbidities	1	0.01	
Clinical symptoms	Dyspnea	4	0.05	12
	CNS symptoms [b]	7	0.09	
	Thoracic pain	1	0.01	
Vital signs	Blood pressure	1	0.01	3
	Respiratory rate	1	0.01	
	Dehydration	1	0.01	
Laboratory test	CRP	2	0.03	12
	LDH	2	0.03	
	ALT	1	0.01	
	D-dimer	1	0.01	
	Lymphopenia	1	0.01	
	Leucocyte count	1	0.01	
	Bandemia	1	0.01	
	Thrombocytopenia	1	0.01	
	Hypoalbuminemia	1	0.01	
	Nosocomial infections	1	0.01	
Imaging	Pneumonia	2	0.03	4
	Abnormal CR or CT	2	0.03	
Treatment [c]	Neuraminidase inhibitors	1	0.01	2
	Statin use	1	0.01	
Score system	Shock index	2	0.03	19
	PaO_2/FiO_2 ratio	4	0.05	
	qSOFA	3	0.04	
	PSI	2	0.03	
	APACHE II	2	0.03	
	iPIT	1	0.01	
	GID	1	0.01	
	STSS	1	0.01	
	SIRS	1	0.01	
	OHPIP	1	0.01	
	ILI-score	1	0.01	
Total (34 articles)	42	77	1.00	77

[a]: The number keeps two decimal places; [b]: Central nervous system; [c]: Reduced mortality.

TABLE 2. GRACE assessment scores by item.

Checklist item	Total (n)	% of total
D1. Were treatment and/or important details of treatment exposure adequately recorded for the study purpose in the data source(s)?	19	56
D2. Were the primary outcomes adequately recorded for the study purpose?	21	62
D3. Was the primary clinical outcome(s) measured objectively rather than subject to clinical judgment?	23	68
D4. Were primary outcomes validated, adjudicated, or otherwise known to be valid in a similar population?	11	32
D5. Was the primary outcome(s) measured or identified in an equivalent manner for the treatment/intervention group and the comparison group?	16	47
D6. Were important covariates that may be known confounders or effect modifiers available and recorded?	8	24
M1. Was the study (or analysis) population restricted to new initiators of treatment or those starting a new course of treatment?	13	38
M2. If one or more comparison groups were used, were they concurrent comparators? If not, did the authors justify the use of historical comparison groups?	18	53
M3. Were important confounding and effect-modifying variables taken into account in the design and/or analysis?	16	47
M4. Is the classification of exposed and unexposed person-time free of immortal time bias?	11	32
M5. Were any meaningful analyses conducted to test the key assumptions on which the primary results are based?	15	44

in accordance with a qualitative judgment by the assessors. Most of the included studies were deemed to be at low risk of bias. Studies rarely were rated as high risk of bias mainly according to the GRACE checklist.

4. Discussion

This systematic review demonstrates that a large number of influenza infection risk prediction models have been developed in the past few decades. We identified 34 studies that reported 42 risk factors, which showed great heterogeneity in the selection and definition of predictive factors. Prognostic models of influenza infection are all available, and they all seem to show good prognostic performance in the study. However, some models have a high risk of bias, and the sample size is too small. In addition, this is because the selection of patients in the group is not representative and the model is overfitting [6, 9, 11, 40]. Therefore, the performance estimates of some models are likely be misleading or optimistic [11, 25, 34, 42]. We have proven that some of the definitions and assessments of risk factors in the research are quite different, which may appear to be the same on the surface, and in many cases, the definitions and assessment methods given in the research lack detailed descriptions [1, 9, 11, 28, 29, 40, 42, 55]. However, even if the definitions of risk factors are the same in models, there are still many differences in detailed descriptions. An analysis of the evaluation methods used in the research shows that the actual standards for performance measurement verification and reporting are not sufficiently optimized. Only a few studies have been externally validated, and some of them are prospective studies [6, 41, 50]. However, neither internal verification nor time verification can detect the general applicability of the model because it requires the use of data from different sources for external verification [58–60].

When developing a model, the target population must also be carefully described to evaluate the performance of the development or verification model, which determines the applicable population of the model when testing and using the model. However, studies included in our systematic review tend to overlook the full description of the research population, which makes users of these models doubt the applicable population of the model. Models developed in different regions and groups may not be suitable for another group and region, especially risk factors that may be different. The clinical application performance of the model in different regions and populations is a particularly valuable indicator for judging its ability [59, 61]. Therefore, it is very important to verify the risk prediction model externally to verify the portability and universality of the model to its region and population cohort [62]. For the comparison of different prediction models, external verification is the best way to determine the predictive ability of the model in independent datasets, although only a few models have been externally verified [60, 63, 64]. A detailed description of the study population can also help us understand the variability of the results of the observed studies, such as mortality related to influenza infection. The variability of prediction results poses important challenges to many prediction models. Data from individual participants in the health care system in different regions may help to better understand the universality and practicability of prediction models in different regions and populations rather than being limited to a certain region and population for development and prediction [65]. This research method can greatly improve the universal applicability and robustness of the prediction model.

As Table 2 illustrates, there are various combinations of risk factors in all risk factor groups, but it is still possible to find a few frequent factor combinations. The most commonly included risk factors are patients with a comorbidity of cardiovascular disease and CNS symptoms on admission, which were used in seven of the 28 models. Both risk factors were included

in most models for which they were considered, consistent with previously identified positive associations. This systematic review determined that comorbidities such as cardiovascular diseases play a key role in the prognosis of influenza-infected patients. According to reports, cardiovascular disease is one of the most important independent risk factors for many viral infections. Influenza virus infection can damage the function of multiple organs, including the lungs, liver, heart and kidneys. Studies have demonstrated that angiotensin-converting enzyme 2 (ACE2) may be the functional receptor for influenza virus to enter human cells. Influenza viruses may increase pulmonary vascular permeability and cause acute lung injury by downregulating ACE2 expression and increasing angiotensin II levels [66–68]. However, the specific mechanism of infection is still unclear, and more studies are needed to confirm that influenza virus infection in patients with cardiovascular disease will accelerate this process [69]. CNS symptoms have been proposed as a clinical sign in prediction models for the prognosis of influenza infection. Previous models have shown that age >65 is an important independent prognostic factor in patients with influenza infection.

From the results of various study reports, it can be seen that there are certain differences in the verification performance of each model. There are also some studies that have not reported any indicators of model performance, although quantitative indicators of model performance are important for evaluating model performance. For various types of performance measurement indicators, the proportion of studies reporting such measures is higher in the subgroups of newer studies than in the subgroups of older studies. For the risk prediction of infected individuals, the discriminative ability of the model is the most basic and most important attribute of the prediction model. Approximately 80% of studies report the discriminative ability of the model. The main indicator is the AUC or c index, but the discriminative ability of many models cannot be effectively applied in clinical practice [1, 3, 6, 28–30, 41, 52, 55].

However, there are several limitations. We only included studies published in English and did not search gray literature, but the missing models due to this are limited in usage and usually of relatively low quality. Most of the studies are retrospective observational studies, small sample sizes, incomplete data, and imbalanced prognostic treatment may all have an impact on predictive performance. These models may represent local practices, but due to the low proportion of patients from international centers, their generality outside the region is limited. Demonstration of the wider applicability of the models will require multiple studies aiming to externally validate them in different cohorts of patients.

5. Conclusions

The prognostic models for patients diagnosed with influenza infections seem to show good to excellent discriminating performance and are usable. However, some models have a higher risk of bias, mainly due to the different criteria for including patients and the definition of risk factors. Therefore, the predictive power of some models may be optimistic and misleading. Future research needs to share data and expertise used to develop, validate and update predictive models related to influenza infection.

ABBREVIATIONS

ED, emergency department; IPPV, invasive positive pressure ventilation ; CXR, chest X-ray; ICU, intensive care unit; PSI, pneumonia severity index; CRP, C-reactive protein; WBC, white blood cell; PMEWS, the Pandemic Medical Early Warning Score; qSOFA, 'quick' sequential organ failure assessment scores; APACHE II, Acute Physiology and Chronic Health Evaluation; ICNARC, Intensive Care National Audit & Research Centre; CURB-65, a score for pneumonia severity; NA, Not Available; IQR, interquartile range; BMI, body mass indes; LDH, lactate dehydrogenase; ALT, alanine transaminase; AUC, area under curve; iPIT, Influenza Pandemic ICU Triage; GID, Geriatric influenza death; STSS, the Simple Triage Scoring System; SIRS, systemic inflammatory response syndrome; OHPIP, Ontario Health Plan for an Influenza Pandemic; ILI-score, the influenza-like illness score.

AUTHOR CONTRIBUTIONS

Conception and design—YS, YZ, SZ. Collection and assembly of data—YS, YZ. Data analysis and interpretation—YS, YZ, SZ. Manuscript preparation—YS. Manuscript proofing and final approval of the manuscript—all authors.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

CONSENT FOR PUBLICATION

Written informed consent for publication was obtained from all participants.

APPENDIX

See Table 3.

TABLE 3. Details of the studies on the prognosis models of influenza.

Source	Study design	Country	Study period	Patient of data collection	NO. of study sites	NO. of patients	Ages	Mortality definition	AUC	Evidence quality[a]
Cvetanovska M, *et al*. [6], 2016	Prospective	Macedonia	2012–2015	Age, sex, living place, vaccine, use of osaltamivir, intensive, mechanic ventilation, comorbid conditions, cardiovascular disease, SAPS 2 score	1	87	54.77 ± 17.3	ICU Dead	0.755	Moderate
Fujikura Y, *et al*. [40], 2014	Retrospective	Japan	2009–2010	Age, sex, and comorbid conditions, IPPV use, treatment options and outcome data	2491	346	NA	ICU Dead	0.82	Low
Capelastegui A, *et al*. [41], 2012	Prospective	Spain	2009–2010	Sociodemographic characteristics, pre-existing medical conditions, vaccinations, toxic habits, previous medications, exposure to social environments, measures to prevent influenza	36	618	48.60 (SD 15.7)	In-hospital	0.77	High
Tai H C, *et al*. [9], 2019	Retrospective	Taiwan	2010–2015	Vital signs, demographic characteristics, influenza subtype, laboratory data, past medical history, admission, and 30-day mortality data	1	409	79.5 ± 8.3	In-hospital	0.77	Low
Schoen K, *et al*. [11], 2019	Retrospective	Brazil	2016	Clinical, laboratorial and radiological data	1	160	43	ICU	NA	Low
Chu S E, *et al*. [1], 2020	Retrospective	Taiwan	2010–2016	Vital signs, blood tests, image reports, diagnosis, treatments, and daily medical records of doctors and nursing staff	1	3561	48.08 ± 19.51	In-hospital	0.861	Low
Chung J Y, *et al*. [28], 2018	Retrospective	Taiwan	2010–2015	Demographic characteristics, vital signs, past history, laboratory data, complications, and outcomes	1	409	79.5 ± 8.3	30-day dead	0.861	Low
Adeniji K A, *et al*. [29], 2011	Retrospective	UK	2009–2010	Demographic data, comorbidity, CXR, ventilatory support, level of care, days, mortality and the physiological and laboratory components	1	62	40.52	In-hospital	0.88	Low
Choi W I, *et al*. [42], 2011	Retrospective	South Korea	2009–2010	Age, sex, intensive, mechanical ventilation, antiviral and antibacterial agents	14	269	48 (Rang 15–93)	In-hospital	NA	Low
Shi S J, *et al*. [55], 2017	Retrospective	China	2009–2014	Characteristics, comorbidities, laboratory and image, vital signs	1	170	55.4 ± 17.7	In-hospital	0.945	Low
Cheung W, *et al*. [43], 2012	Prospective	New Zealand; Australia	2009–2010	Ontario Health Plan for an Influenza Pandemic (OHPIP) triage protocols	8	805	NA	ICU	NA	High

TABLE 3. Continued.

Source	Study design	Country	Study period	Patient of data collection	NO. of study sites	NO. of patients	Ages	Mortality definition	AUC	Evidence quality[a]
Chang S H, *et al*. [3], 2019	Retrospective	Taiwan	2010–2015	Demographic data, vital signs, past histories, influenza subtypes, treatment outcomes, radiographic findings, readmission rates and qSOFA	1	409	79.5 ± 8.3	30-days dead	0.81	Low
Morton B, *et al*. [25], 2017	Retrospective	UK	2010–2011	Demographics, comorbidities, physiological observations, clinical laboratory tests, arterial blood gases and oxygen saturations	1	86	NA	NA	0.88	Low
Pawelka E, *et al*. [56], 2018	Retrospective	Austria	2017–2018	Demographic data, laboratory results, symptoms, treatment and underlying medical conditions	1	396	75.5 (Rang 63–84)	In-hospital 90-day dead	NA	Low
Chung J Y, *et al*. [30], 2019	Retrospective	Taiwan	2010–2015	Demographic data, vital signs, shock index, past histories, subtypes and outcomes	1	409	79.5 ± 8.3	30-day dead	0.62	Low
Ho Y C, *et al*. [24], 2009	Retrospective	Taiwan	2001–2007	Demographics, symptoms, hospitalization, the presence of sepsis, severe sepsis, laboratory values, virus isolation, antiviral treatment and vaccination	1	225	52 (Rang 17–89)	In-hospital	NA	Low
Muller M P, *et al*. [51], 2010	Retrospective	Canada	2005–2007	Demographic, clinical, laboratory and radiographic data	25	617	76 (Rang 64–83)	ICU In-hospital	0.8	Low
Rodriguez-Noriega E, *et al*. [44], 2010	Retrospective	Mexico	2009	Demographics, signs and symptoms, history of health care utilization, chronic medical conditions, laboratory and radiology findings	1	1840	29 (Rang 22–41)	NA	NA	Low
Zhang P J, *et al*. [45], 2013	Retrospective	China	2009	Demographic information, underlying conditions, vaccination status, medication, complications and outcomes	426	2151	34.0 (IQR 24.1–50.6)	In-hospital	NA	Low
Cho W H, *et al*. [26], 2011	Retrospective	South Korea	2009	Demographic data, PSI, CURB65, risk factors, time to first dose of antiviral medication, routine laboratory data, clinical outcome and radiological characteristics	2	37	46.1 ± 17.3	In-hospital	NA	Low
Riquelme R, *et al*. [46], 2011	Retrospective	USA	2009	Demographic data, history and physical findings, comorbidities, laboratory characteristics	22	250	43.3	In-hospital	0.78	Low
Pereira J M, *et al*. [47], 2012	Prospective	Spain	2009	Demographics, comorbid conditions, physiological status and organ supports	33	265	42 ± 16.1	ICU	0.73	High
Bjarnason A, *et al*. [54], 2012	Prospective	Iceland	2008–2009	Sputum, blood cultures, PSI, CURB-65 and APACHE II scores	1	114	44.0 (95% CI 37.1–50.9)	ICU	NA	Low

TABLE 3. Continued.

Source	Study design	Country	Study period	Patient of data collection	NO. of study sites	NO. of patients	Ages	Mortality definition	AUC	Evidence quality[a]
Commons R J, *et al*. [48], 2012	Retrospective	Australia	2009	Clinical characteristics, comorbid conditions, potential infection, symptoms, treatment, PSI, CURB-65 and SMRT-CO severity scores	7	112	42 (Rang 15–79)	ICU	0.83	Low
Kiliç H, *et al*. [49], 2015	Retrospective	Turkey	2009	Age, sex, duration, fever, CRP, sedimentation rate, WBC counts, platelet counts, monocytosis, leukocytosis, D-dimer levels, CURB-65 scores, comorbid illnesses and radiological findings	1	75	56.5 (Rang 17–85)	ICU In-hospital	NA	Low
Challen K, *et al*. [52], 2007	Retrospective	UK	2005	Clinical characteristics, PMEWS, CURB-65	1	144	NA	In-hospital	0.944	Low
Brandão-Neto R A, *et al*. [50], 2012	Prospective	Spain	2009	Underlying medical conditions, laboratory tests, radiographic findings, pneumonia severity, treatment course, in-hospital death, ICU admission, invasive mechanical ventilation, vasopressor use, renal failure at the admission and during the follow-up	1	53	43	ICU In-hospital	NA	Moderate
Atamna A, *et al*. [39], 2021	Retrospective	Israel	2017–2018	baseline demographics, BMI (kg/m^2), Comorbidities, hypertension, ischemic heart disease, congestive heart disease, chronic obstructive pulmonary disease, chronic kidney disease, liver disease, malignancies, and organ transplantations	1	512	74 (Rang 62–83)	30-day dead	NA	Low
Louie J K, *et al*. [35], 2011	Retrospective	USA	2009	Height, weight, demographic characteristics, clinical presentation and course, comorbid conditions, and laboratory and radiographic findings, hospital admission, infectious disease, radiographic and microbiologic studies, transfers, and hospital discharges onto a standardized case report form	1	534	46 (Rang 20–92)	Dead	NA	Low
Demirjian S G, *et al*. [37], 2011	Retrospective	USA	2009	Demographic, clinical, and outcome data	1	89	46 without AKI; 49 with AKI	Dead	NA	Low

TABLE 3. Continued.

Source	Study design	Country	Study period	Patient of data collection	NO. of study sites	NO. of patients	Ages	Mortality definition	AUC	Evidence quality[a]
Wong C M, *et al*. [34], 2013	Retrospective	China	1998–2001	Baseline data, lifestyle habits (smoking history, exercise frequency and alcohol drinking), socioeconomic status (housing type, education and monthly expenditure) of all the subjects	18	66820	NA	Dead	NA	Low
Lopez-delgado J C, *et al*. [36], 2013	Prospective	Spain	2009–2011	Demographic, clinical, and outcome data	2	114	49.2 ± 14	Dead	NA	Moderate
Rowan K M, *et al*. [38], 2016	Retrospective	Iran	2009	Demographics, occupation, ethnicity, physical examination, blood pressure, height and weight	1	55	NA	ICU Hypoxemia	NA	Low
Rowan K M, *et al*. [53], 2010	Retrospective	UK	2007–2010	Age, sex, source of admission to the critical care unit, APACHE II, ICNARC physiology score, CURB-65	221	562	58.8	ICU In-hospital	NA	Low

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