Original Article

Prognostic Indicators for Heart Failure Hospitalization in Acute Coronary Syndrome Patients: An Observational Study under the Influenza Vaccination Trial

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Background: Heart failure [HF] is described as a consequence from tissue injury in myocardial infarction through finally organ failure. Therefore, HF prevention through forecasting clinical predictors is useful for closely HF monitoring and management.

Objective: To explore prognostic indicators for HF hospitalization in Acute coronary syndrome [ACS] patients through the influenza vaccination trial.

Materials and Methods: These observational data were collected from 439 ACS patients of Phrommintikul et al. The inactivated influenza vaccine was injected intramuscularly as a single dose in the vaccination group. The HF hospitalization outcome was determined through one-year follow-up time. The multivariable Cox's regression model was performed to explore the prognostic values.

Results: The significant prognostic indicators were female (HR 4.05, 95% CI 1.25 to 13.19, $p = 0.020$), dyslipidemia (HR 7.44, 95% CI 1.88 to 29.40, $p = 0.004$), elevated SCr (HR = 5.46, 95% CI 1.39 to 21.41, $p = 0.015$), impaired LVEF (HR 9.55, 95% CI 2.55 to 35.81, $p = 0.001$), and influenza vaccination (HR 0.25, 95% CI 0.07 to 0.86, $p = 0.028$).

Conclusion: ACS patients who were female with dyslipidemia, elevated SCr, and impaired LVEF should be closely monitored for HF. The influenza vaccination had a significant protective effect for HF in ACS. Therefore, the benefit of influenza vaccine should be considered in practice for ACS patients.

Keywords: Influenza vaccine, Acute coronary syndrome, Heart failure, Prognostic indicators

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Acute coronary syndromes [ACSs] are a major cause of life-threatening disorders in emergency care and hospitalization(1). One of the most common in-hospital outcomes in ACS patients is heart failure [HF]. HF is described as a consequence from tissue injury in myocardial infarction [MI] through organ failure. Therefore, HF prevention through forecasting clinical predictors is useful for closely monitoring and management.

Several predictors in ACSs have been well proven and treatments such as beta-blockers, statins, angiotensin-converting enzyme inhibitors [ACEIs] or angiotensin II receptor blocker [ARBs], anti-thrombotics, as well as coronary revascularization(1) are recommended.

Influenza vaccination has provided benefits in hospitalization caused by cardiovascular diseases(2) or cerebrovascular diseases(2) in elderly. Furthermore, evidences from randomized control trials showed

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a reduction of major adverse cardiovascular events in coronary artery disease [CAD] patients[3] after influenza vaccination. Moreover, influenza vaccination is recommended as a secondary prevention in patients with CAD, atherosclerotic vascular disease, and chronic HF. However, to our knowledge, there has not been any study done about influenza vaccine as a clinical predictor for HF. Therefore, the purpose of the present study was to explore clinical predictors for hospitalization due to HF in ACSs as part of the influenza vaccination trial.

Materials and Methods

Data sources and data collection

Observational data was collected from 439 ACS patients age above 50 years old from Phrommintikul et al[3], which was a prospective, randomized, open with blinded endpoint study. Patients with serum creatinine higher than 2.5 mg/dL, hemoglobin lower than 10 g/dL, liver disease, cancer, or life expectancy less than one year were excluded. The vaccination group was given a single-dose intramuscular injection of 0.5 mL inactivated influenza vaccine. Patients were randomly assigned to the vaccination group. All patients received standard treatment in the tertiary care university hospital by primary cardiologists. The outcome was defined as hospitalization due to HF. The follow-up duration was about 12 months and verified by the cardiologists.

Definition

A chest pain longer than 20 minutes with ST-segment elevation of EKG in two consecutive leads or more was described as an acute ST-segment elevation myocardial infarction [STEMI]. A chest pain with longer than 20 minutes with cardiac troponin or creatine kinase-muscle/brain [CK-MB] rising without ST-segment elevation was defined as a non-ST-segment elevation myocardial infarction [NSTEMI]. Having a chest pain at rest without cardiac troponin or CK-MB rising was defined as an unstable angina [UA]. While, non-ST-segment elevation ACS [NSTE-ACS] comprised NSTEMI and UA.

Patients with estimated glomerular filtration rate [eGFR] less than 60 ml/minute/1.73 m^2 were described as chronic kidney disease [CKD]. Patients who had serum level of low density lipoprotein [LDL] of more than 130 mg/dL, triglyceride [TG] higher than 150 mg/dL, high density lipoprotein [HDL] lower than 35 mg/dL, or had been treated with lipid lowering agents were assigned as dyslipidaemia.

Data analysis

The patient's characteristics of HF hospitalization were compared with those who were event-free. The continuous characteristic data were classified into categorical data (e.g., age, serum creatinine [SCr], and left ventricular ejection fraction [LVEF]) and tested via Fisher's exact test. An exploratory model concept was conducted to investigate the prognostic indicators and univariable analysis was performed. The reduced model of prognostic indicators was analysed as multivariable hazard ratio [HR] by Cox's regression.

In case of missing data of continuous variables, the multiple imputation technique would be used to address the missing data via chained equation method[4,5]. Although the multiple imputation by chained equation was a principle method, the limitation of numbers and distribution of missing data should be of concern. For this reason, the imputed data would be categorized to binary data for proper management.

The primary endpoint of Phrommintikul et al[3] was any cardiovascular events, including death, ACS hospitalization, stroke hospitalization or HF hospitalization. The sample size calculation of was based on 1-year follow-up of the Flu Vaccination for Acute Coronary Syndrome [FLUVACS] study[6] where major adverse cardiovascular events of 37% in the control, and 22% in active arm were revealed. The level of significance was set at 5%, the power at 80%, and the rate of loss to follow-up at 5%, thus, 210 patients were required in each group.

Ethical approval

The present study was approved by the Ethics Committee, the faculty of Medicine, Chiang Mai University.

Results

Patient's characteristics

The present observational study collected data of the 439 ACS patients with 151,611 patient-days of follow-up time. Half of the patients were over 65 years old with 249 (56%) male gender as presented in Table 1. The proportions of patients' comorbidity, described as hypertension [HT], diabetes mellitus [DM], dyslipidemia, chronic obstructive pulmonary disease [COPD], and history of CKD, were 60.4%, 30.5%, 46.9%, 3.0%, and 4.56%, respectively. Diagnosed ACS patients were classified as 159 (36.2%) of STEMI and 280 (63.8%) of NSTE-ACS. Four-fifth (79.25%) of the patients with STEMI reached reperfusion therapy, and more than half of NSTE-ACS patients (53.21%)

Table 1. ACS patients' characteristics for HF hospitalization (n = 439)

Characteristics	HF hospitalization (n = 14), n (%)	Without HF hospitalization (n = 425), n (%)	*p*-value
Age (year)			0.281
≤65	5 (35.71)	214 (50.35)	
>65	9 (64.29)	211 (49.65)	
Male	5 (35.71)	244 (57.41)	0.107
HT	10 (71.43)	255 (60.00)	0.390
DM	7 (50.00)	127 (29.88)	0.108
Dyslipidemia	11 (78.57)	195 (45.88)	0.016
COPD	1 (7.14)	12 (2.83)	0.348
Smoking	0 (0.00)	48 (11.29)	0.183
Prior MI	2 (14.29)	16 (3.76)	0.051
History of CKD	4 (28.57)	16 (3.76)	<0.001
SCr (mg/dL)			0.028
≤1.1	3 (21.43)	218 (51.29)	
>1.1	11 (78.57)	207 (48.71)	
Type of ACS			0.545
NSTEMI & UA	10 (71.43)	270 (63.53)	
STEMI	4 (28.57)	155 (36.47)	
Reperfusion or Revascularization			0.034
No	9 (64.29)	155 (36.47)	
Yes	5 (35.71)	270 (63.53)	
LVEF (%)			<0.001
>40	3 (21.43)	296 (69.65)	
≤40	11 (78.57)	129 (30.35)	
Medication			
Aspirin	14 (100)	413 (97.18)	0.524
β-blockers	9 (64.29)	316 (74.35)	0.398
CCBs	2 (14.29)	70 (16.47)	0.828
ACEIs/ARBs	5 (35.71)	252 (59.29)	0.078
Statins	9 (64.29)	284 (66.82)	0.843
Influenza vaccination	4 (28.57)	217 (51.06)	0.098

DM = diabetes mellitus; HT = hypertension; COPD = chronic obstructive pulmonary disease; MI = myocardial infarction; CKD = chronic kidney disease; SCr = serum creatinine; HF = heart failure; ACS = acute coronary syndrome; STEMI = ST-segment elevation myocardial infarction; NSTEMI = non-ST-elevation myocardial infarction; UA = unstable angina; LVEF = left ventricular ejection fraction; CCBs = calcium channel blockers; ACEIs = angiotensin-converting enzyme inhibitors; ARB = angiotensin II receptor blockers

received coronary revascularization. The most common medications were aspirin (427, 97.3%), beta-blockers (325, 74.0%), angiotensin converting enzyme inhibitors [ACEIs] or angiotensin receptor blockers [ARBs] (257, 58.54%), and statins (293, 66.7%).

Factors affecting HF hospitalization

The clinical profiles of ACS patients hospitalized due to HF and those who were not, did not differ (Table 1), excepted for dyslipidemia (78.57% and 45.88%, $p = 0.016$), history of CKD (28.57% and 3.76%, $p<0.001$), elevated SCr (78.57% and 48.71%, $p = 0.028$), reperfusion or revascularization receiving (35.71% and 63.53%, $p = 0.034$) and impaired LVEF (78.57% and 30.35%, $p<0.001$).

The results from univariable analysis showed the prognostic trend for dyslipidaemia, history of CKD, elevated SCr, impairment of LVEF, and the procedure of reperfusion or revascularization (Table 2). However, the prognostic variable of reperfusion or revascularization procedure disappeared after multivariable analysis was taken.

For univariable analyses, the results showed that no smoking patient in one of the contrast group of HF hospitalization, and most ACS patients (427, 97.3%) had received aspirin. These two factors were causes of under estimable results (Table 2).

After all data were analysed by the multivariable Cox's regression model, five prognostic indicators were revealed (Table 3). Clinical predictors for hospitalization due to HF included female patients (HR 4.05, 95% CI 1.25 to 13.19, $p = 0.020$), dyslipidaemia (HR 7.44, 95% CI 1.88 to 29.40, $p = 0.004$), elevated SCr (HR 5.46, 95% CI 1.39 to 21.41, $p =$

Table 2. Univariable hazard ratios of prognostic indicators for HF hospitalization (n = 439)

Characteristics	HR	95% CI	*p*-value
Age >65 years old	1.83	0.61 to 5.45	0.280
Female	2.46	0.82 to 7.33	0.107
HT	1.66	0.52 to 5.29	0.392
DM	2.31	0.81 to 6.58	0.118
Dyslipidemia	4.23	1.18 to 15.15	0.027
COPD	2.46	0.32 to 18.81	0.385
Smoking	NE	NE	NE
Prior MI	3.98	0.89 to 17.79	0.071
History of CKD	8.71	2.73 to 27.77	<0.001
SCr >1.1 mg/dL	3.82	1.06 to 13.68	0.040
Type of ACS: STEMI	0.72	0.23 to 2.31	0.586
Reperfusion or revascularization	0.33	0.11 to 0.99	0.047
LVEF ≤40%	8.15	2.27 to 29.21	0.001
Medication			
Aspirin	NE	NE	NE
β -blockers	0.63	0.21 to 1.87	0.400
CCB	0.84	0.19 to 3.76	0.822
ACEIs/ARBs	0.38	0.13 to 1.14	0.083
Statins	0.90	0.30 to 2.68	0.849
Influenza vaccination	0.39	0.12 to 1.24	0.110

HR = hazard ratio; CI = confidence interval; DM = diabetes mellitus; HT = hypertension; COPD = chronic obstructive pulmonary disease; MI = myocardial infarction; CKD = chronic kidney disease; SCr = serum creatinine; HF = heart failure; ACS = acute coronary syndrome; STEMI = ST-segment elevation myocardial infarction; LVEF = left ventricular ejection fraction; CCBs = calcium channel blockers; ACEIs = angiotensin-converting enzyme inhibitors; ARB = angiotensin II receptor blockers; NE = not estimable

Table 3. Multivariable Cox's regression analysis of prognostic indicators for HF hospitalization; the reduced model

Prognostic Indicators	HR	95% CI	*p*-value
Female	4.05	1.25 to 13.19	0.020
Dyslipidemia	7.44	1.88 to 29.40	0.004
SCr >1.1 mg/dL	5.46	1.39 to 21.41	0.015
LVEF ≤40%	9.55	2.55 to 35.81	0.001
Influenza vaccination	0.25	0.07 to 0.86	0.028

HR = hazard ratio; CI = confidence interval; LVEF = left ventricular ejection fraction; HF = heart failure; SCr = serum creatinine

0.015), and impaired LVEF (HR 9.55, 95% CI 2.55 to 35.81, $p = 0.001$). Received influenza vaccination was shown as a potential protective indicator (HR 0.25, 95% CI 0.07 to 0.86, $p = 0.028$).

Discussion

The present post hoc study disclosed five clinical predictors as profiles for patients who were hospitalized due to HF. They included female patients who had dyslipidaemia, elevated serum creatinine, impaired LVEF, and received influenza vaccination.

Gender

Male was indicated as a major risk for HF, and a predictor for mortality and composite outcome of death or non-fatal MI[7]. In contrast, female was more likely to have increasing risk of obesity[8], poor exercise or physical inactivity[8], disadvantaged socioeconomics, and suffering from depression[9], which these factors contributed to the risk of cardiovascular disease.

Female, a gender variable in FLUCAD study, was demonstrated as a predictor of coronary ischemic events such as cardiovascular death, MI, coronary revascularization, or hospitalization for myocardial ischemia. Women had worse prognosis of ACS, but were not an independent relation with mortality[10]. Despite this, some studies showed that female was an independent predictor for mortality in short-term follow-up[11] while male was a predictor for long-term follow-up[11]. In summary, the adverse outcomes could be due to the variations of population and baseline characteristics than the gender variable itself[10]. However, women with acute STEMI showed higher risk for complicated congestive HF than men, as disclosed in a tertiary care university hospital[12].

Dyslipidemia

Dyslipidemia is associated with an increased risk of HF[13]. Increasing ratio of total cholesterol to high-density lipoprotein cholesterol showed higher risk of HF[13]. Therefore, lipid disorder management is recommended, such as using statin therapy for prevention of cardiovascular event and new-onset HF. Statin can reduce non-fatal cardiovascular event, which includes reduction of non-fatal MI, coronary revascularization, or stroke, and reduces cardiac causes and all causes mortality[14] from coronary heart disease in controlled group. Additionally, statin is indicated as a protective predictor for composite outcome of death, MI, and stroke.

Impaired LVEF

The appearance of asymptomatic LV dysfunction can lead to HF and other cardiovascular events[15], and increase risk of progression to congestive HF[15]. An increased LVEF was shown as a protective factor for readmission of congestive HF in one year after ACS[16]. In addition, impaired LVEF was also demonstrated as a clinical predictor for mortality[17].

Renal function

Rising serum creatinine and CKD were factors predicting the deterioration of renal function. The reduction of renal function would decrease glomerular filtration in patients with HF[18], and the deterioration of renal function further contributed to decompensated HF. A previous study described that an increasing serum creatinine level was a predictor in elderly with congestive HF[19]. The deterioration of renal function could affect treatment options to reach cardiovascular benefits[18]. These information confirmed that renal function was a powerful independent predictor in HF[18], while CKD[20,21] and elevated serum creatinine[22] were predictors for mortality and cardiovascular events.

Influenza vaccination

The evidence had shown that seasonal patterns of cardiovascular deaths was similar to the patterns of influenza circulation[23]. In addition to clinical symptoms, influenza infection can cause systemic effects in patients, such as myalgia, high fever, fatigue and it could induce MI[23]. The influenza virus has extensive effects on inflammatory and coagulation pathways, which lead to destabilize the atherosclerotic plaques and cause coronary occlusion, resulting in acute MI[23]. Host responses to acute infections not only can facilitate ACS inflammatory and thrombogenic changes, but they also affect coronary arteries and atherosclerotic lesions, such as increased sympathetic activity[24].

In MI patients, influenza vaccination showed reduction of cardiovascular death[6], re-hospitalization[3], and decline in cardiovascular composite outcomes, such as double end-point (cardiovascular death and MI), triple end-point (re-hospitalization, cardiovascular death, and MI)[6] and major adverse cardiovascular events (death, hospitalization for ACS, hospitalization for HF, and hospitalization for stroke)[3].

In addition, influenza vaccine also reduced the composite cardiovascular outcomes in patients with CAD, such as coronary ischemic event including cardiovascular death, MI, coronary revascularization, or hospitalization for myocardial ischemia[25].

Furthermore, mortality reduction after influenza vaccination was also demonstrated in elderly with chronic heart disease[26] and healthy elderly with underlying medical conditions[27]. Particularly, the decline of re-hospitalization[3] indicated that influenza vaccination was a predictor for hospitalization for ACS. The additional observational studies in elderly who received the influenza vaccine showed a reduction of hospitalized cerebrovascular disease[2], hospitalized ischemic heart disease[2], and hospitalized for congestive HF[2].

Moreover, influenza vaccination was shown to lower the risk for all-cause mortality compared to no vaccination in patients with chronic HF. However, this association was causal or cannot be determined[28]. Nevertheless, some evidences showed incomplete match influenza vaccine could be effective against disease and severe outcome and provide protection in frail elderly[29] or in high-risk medical conditions[30].

Limitation

Incomplete data were limitations of the present study. From 20 variables, only two incomplete variables were found. The variables of SCr and LVEF had 6.83% and 54.67% of missing values, respectively. However, the multiple imputations technique was conducted, and imputed data were categorized for appropriate management. These variables should be monitored in a further large study as well.

Conclusion

Patients with ACS who were female presented with dyslipidaemia, high level of serum creatinine, and impaired LVEF should be closely monitored for hospitalization for HF. The findings from the present study showed a potential protective effect of the influenza vaccination for ACS patients hospitalized due to HF. Additionally, the benefit of influenza vaccination should be acknowledged in clinical routine practice for ACS patients and studies in a larger population should be explored.

What is already known on this topic?

Several predictors in ACSs have been well-proved and recommended for treatment such as, beta-blockers, statin, angiotensin-converting enzyme inhibitors, antithrombotic, coronary revascularization as well as influenza vaccination.

Although the influenza vaccination has been reported to reduce recurrent hospitalization for ACS and major adverse cardiovascular events in ACS patients, its benefit and other prognostics for HF hospitalization still does not exist.

What this study adds?

This study describes significant prognostic indicators for HF hospitalization in ACS patients, such as female, dyslipidaemia, rising serum creatinine, impaired LVEF, and especially the added benefit of influenza vaccination, which should be strongly acknowledged in clinical routine practice for ACS patients monitoring.

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Potential conflicts of interest

The authors declare no conflict of interest.

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