Original Article:

Effect of training after discharge on re-admission and re-hospitalization of patients with heart failure (randomized single-blind clinical trial)

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ABSTRACT

Discharge is the process of transferring a patient from hospital which involves a transfer of responsibility from inpatient service providers or hospitalist to the patient and primary care physicians. Inappropriate follow up after discharge will increase the risk of re-admission and re-hospitalization which leads to the poor performance of the health system. The aim of this study was to determine the effect of physician's caring after discharge on re-admission and referral to doctors.
This study was conducted as a clinical trial on patients with early intervention for educational instruction. The clinical trial was conducted at a later stage on 120 patients with heart failure who were hospitalized in Taleghani Hospital, Tehran. For a period of five months after discharge, using block randomization, the subjects were divided into two groups, including intervention and control groups. At the time of discharge, the patients in the intervention group received instructions and were trained by physicians, while no intervention was applied for the subjects in the control group**.** In addition to demographic questions, the patients were asked about two main outcomes, i.e. "re-admission" and "referral to doctors". To collect the required data, the subjects in both groups were contacted via telephone calls (nine times) every week in the first month after discharge and two times per week in the following two months. Generalized linear mixed effects model method was used for evaluating the effect of physicians caring after discharge on re-admission and re-hospitalization.
The results of this study showed that with the passage of time (weekly) after discharge, there was a significant increase in the rate of re-admission in the control group, while there was no significant increase in re-hospitalization. There was no statistical evidence showing a significant difference between the rates of re-admission along with the time in the treatment intervals. In other words, the patients in the control group experienced a significant increase in the odds ratio of re-admission over the time.

Key words: training; readmission; re-hospitalization; heart failure

INTRODUCTION

Cardiovascular diseases are a group of disorders affecting heart and blood vessels, consisting of coronary heart disease, cerebrovascular disease, high blood pressure, peripheral artery disease, rheumatic heart disease, congenital heart disease and heart failure. Heart failure (HF), sometimes known as congestive heart failure, occurs when heart muscle doesn’t pump blood properly [1]. Certain conditions, such as narrowed arteries of heart or high blood pressure gradually weaken the heart which prevents it from pumping blood efficiently. The risk factors for heart failure are high blood pressure, coronary disease, heart attack, diabetes or some diabetes medications, alcohol and tobacco use, etc. [2]. Complications of heart failure depend on the cause and the severity of the disease, overall health, and other factors such as age. Some of the complications are: kidney damage or failure, heart valve problems, heart rhythm problems, and liver damage [3]. HF has been singled out as an epidemic and is an overwhelming clinical and public health problem, associated with significant mortality, morbidity, and healthcare expenditures, particularly among those aged over 65 years [4]. HF is a common, costly and potentially fatal condition. In developed countries, around 2% of adults aged over 65 years old are affected by HF, which has recently increased up to 6-10%. This illness is a major public health problem, with a prevalence of more than 5.8 million cases in the USA and more than 23 million cases worldwide. The rate of mortality in patients with heart failure is high; even about 50% of patients who can access the best available treatments die within five years since the time of diagnosis. Furthermore, it places a massive burden on patients, their families, and society as a whole [5]. Despite the progresses made in reducing HF-related mortality, hospitalization due to HF is still frequent and the rate of re-admissions continues to rise. Based on estimates, one out of four heart failure patients aged 65 and more are re-hospitalized within 30 days of discharge. Up to 44% of heart failure patients hospitalized in Europe were re-hospitalized at least once within 12 months after discharge. Discharge is the process of transferring a patient from hospital which involves a transfer of responsibility from the inpatient service providers or hospitalist to the patient and primary care physicians [6]. Days after discharge from the hospital are considered to be critical and high-risk because other types of therapy or other conditions such heart disease may have serious adverse effects on the health of the patient and affect his / her clinical status. Nowadays, re-admission results in a decrease in health system performance [7]. The reduction in re-admission rate reduces health care costs [8]. According to a study in America, re-hospitalizations within a month after discharge imposes a financial burden of $17.4 billion [9]. Adverse events in hospitalized patients may occur during the transmission of patient care from one hospital physician to another one; thus, communication between physicians working in hospital may decrease adverse events [10]. The same risk may happen immediately after hospital discharge, so re-admission after hospitalization is a common health problem [7, 11]. It is estimated that 46% of medication errors occur during admission or discharge when orders are written for patients [12]. The results of a study in a multisite Canadian teaching hospital showed that 72% of adverse effects after discharge were attributed to side effects, about half of which were preventable via communication between patient and doctor [11]. Thus, the utilization of discharge survey in medication correction process resulted in a reduction in errors occurring after patients discharge from hospital [12]. Physician's caring for hospitalized patient are discharge plans that include medication orders to be continued after discharge, scheduled outpatient test, and test results that are pending at discharge which must be followed up by the outpatient service providers [10]. Longitudinal data should be analyzed in way to take into account the specific variance caused by repeated measurements. Assessing two or more correlated longitudinal response variables over time generates another type of variance which requires joint methods. Joint modeling of responses makes it possible to evaluate response variables using several covariates and factors while the interaction between the responses is considered. Joint modeling methods results in smaller standard errors of coefficients and hence provides more accurate estimates [13]. Several studies have applied longitudinal univariate and joint methods to analyze medical data [14-18].

This study is conducted to determine the effect of physicians caring after discharge on re-admission and referral to doctor, using generalized linear mixed effects models.

METHODS

This study was conducted as a clinical trial on patients with early intervention for educational instruction in a special edition based on the patient's physician and guidelines in other countries and were collected and compiled according to the needs of the patients. The clinical trial was conducted on 120 patients with heart failure, including 37 female and 83 male patients who were hospitalized in Taleghani Hospital, Tehran. For a period of five months after discharge, using block randomization the subjects were divided into two groups, including intervention and control groups. At the time of discharge, the patients in the intervention group received instructions and were trained by physicians in prevention clinic, but no intervention was applied for the control group. In addition to demographic question, the subjects were asked about two main outcomes, i.e. re-admission and referral to doctor. To collect the required data, the subjects in both groups were contacted via telephone calls (nine times) every week in the first month after discharge and once every two weeks in the following two months. Using a checklist, patient's data were registered fortnightly for three months. Generalized linear mixed effects models method was used to evaluate the effect of physicians caring after discharge on re-admission and re-hospitalization. Among different kinds of models, Generalized Linear Mixed effects Models (GLMMs) are a generalization of generalized Linear Models (GLM) which deals with the Intraclass Correlation (ICC) caused by longitudinal repeated measurements using random effects in the model. This model provides subject specific interpretation as well as data on population average. In this study, random intercepts in the models were used to deal with the difference between patients (or the correlation between repeated measurements for the same patient). They were used to cope with the difference between patients at the baseline. The model can be presented as follows, where $g(E(y_{ij}|b_i))$ is a function which links the mean response given the random intercept for the subject i at the occasion j to the $x_{\acute{\imath}\jmath}$ which is the matrix of covariates and factors, β is the vector of coefficients and b_i is the vector of random intercepts for the subject i:

$$g(E(y_{ij}|b_i)) = x_{\acute{\imath}\jmath}\beta + b_i$$

Moreover, logit link function was used for the dichotomous response variables; it provides straightforward interpretation of the results using odds ratio. Through assessing the ICC caused by the repeated measurements over time for the same subject, it is found that the variation of the responses in the multivariate model is due to the differences between patients, not the residual errors of the model.

STATISTICAL ANALYSIS

Multivariate Analysis

The aim of multivariate models is to answer this question: how can the association among response variables affect the impact of multiple independent variables on them? In other words, when assessing the effect of covariates and factors on response variables, a multivariate model can be used to consider the association between multiple response variables and put them in a single model which yields to valid and precise results. The bivariate model can be presented as follows:

$$\begin{pmatrix} logit(pr(Y_{1ij} = 1|X_{ij}, w_i)) \\ logit(pr(Y_{2ij} = 1|X_{ij}, b_i)) \end{pmatrix} = \begin{pmatrix} x_{\acute{\imath}\jmath}\alpha + w_i \\ x_{\acute{\imath}\jmath}\beta + b_i \end{pmatrix} + \begin{pmatrix} \varepsilon_{1ij} \\ \varepsilon_{2ij} \end{pmatrix}$$

In the multivariate model, the random intercepts in each sub-model, b_i and w_i had a bivariate normal distribution with zero means, special variances and correlation term ρ which takes the correlation between the two response variable into account. Besides, the residual errors ε_{1ij} and ε_{2ij} had a normal distributions with mean zero and different variances separately.

$$\begin{pmatrix} b_i \\ \mathrm{w_i} \end{pmatrix} \sim \mathrm{normal}\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma_b^2 & \rho\sigma_b\sigma_w \\ \rho\sigma_b\sigma_w & \sigma_w^2 \end{pmatrix}\right)$$

$$\begin{pmatrix} \varepsilon_{1ij} \\ \varepsilon_{2ij} \end{pmatrix} \sim \mathrm{normal}\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma_1^2 & 0 \\ 0 & \sigma_2^2 \end{pmatrix}\right)$$

The variance covariance matrix of the response variables can be used to find the correlation between the two response variables. At the end of this article, the determinate effect of training and caring after discharge on re-admission and re-hospitalization of patients with heart failure is presented.

Sensitivity (SE), specificity (SP) and diagnostic accuracy (DA) were used to evaluate the predicted category of binary response variables in both univariate and multivariate models. Moreover, McNemar's test was used to evaluate the differences between the methods in terms of the proportions. The univariate and multivariate results were compared using likelihood ratio test (categorical data analysis ref). The SAS version 9.2 and R statistical software version 3.1.3 were used to analyze the data.

RESULTS

A total of 120 patients were enrolled into this study (69.2% male); the mean age of the subjects was 65.39±8.477 years ranging from 45 to 90 years of age. As shown in table 1, there was a match between the patients in the two groups in terms of sex, age, duration of disease, and level of education.

Table 1. Demographic characters of patients in the two group

Group	Age	Duration of Disease	Years of schooling
Intervention	64.65	3.73	7.80
Control	66.13	3.70	7.12
P-value	t test=0.34	t test=0.95	t test=0.42

In addition, the distribution of response variables in several time points is shown in Table 2.

The results of univariate and joint models are presented in Table 2. The results of univariate models showed that the odds ratio of re-admission of the control group at the baseline was exp(2.038)=7.67 times more than that of the treatment group (p=0.063) while the odds ratio of referral was exp(0.941)=2.56. With a unit of increase in time in control group, the odds ratio of being readmitted increased by 1.068 and 1.658 for physician referral, which were not significant. Odds ratio in the treatment group at each time was exp(-2.038+0.164*time) (.e.g. for time 2 it was exp(-2.038+0.164*2)=0.181) which was not statistically significant. The odds ratio of referral in treatment group was exp(-0.941+0.125*time) which was significant. In other words, the odds ratio of referral at each time point and in the treatment group was always less than that in the control group. After adjusting the association between the two response variables using multivariate generalized linear mixed-effects model, the odds ratio of re-admission was not statistically different between the two groups over time (p=0.211), while the intervention had a significant impact on physician referral over time (p=0.020). The odds ratio of re-admission in the control group at the baseline was significantly exp(1.884)=6.62 times more than that in the treatment group (p=0.049); it was also true for physician referral (p=0.010) with the odds ratio of exp(1.041)=2.83. The significant development of re-admission by one unit increase in time at control group was multiplied to 1.453 (p<0.001) while the treatment group did not experience any statistical difference (p=0.211). Contrary to re-admission, the odds ratio of physician referral did not increase significantly in the control group (p=0.408) while with a unit of increase in time, the odds ratio had statistically differed in each time as exp(-1.041+0.189*time).

The random intercepts in univariate models were significant, expressing considerable variation between cases at the baseline; however, after adjusting for the association between the two responses, the variation was only due to the re-admission, not physician referral (p=0.074). The results showed that the intraclass correlation of patients re-admission in the multivariate model was the same in the univariate model, while physician referral became higher in multivariate (in comparison to the univariate model) which can be considered as an outperformance of the multivariate model due to the lower frequency of model residual errors. The correlation between the random intercepts in the model was statistically significant (correlation=0.905, p<0.001). Using the terms in the response variance formula, the significant correlation between the two response variables in the multivariate model was calculated as 0.311 (P<0.001). Table 4 presents a comparison of sensitivity, specificity, and accuracy. Based on the results, multivariate analysis showed a better accuracy in predicting re-admission (ACC for multivariate and univariate models were 0.90 and 0.87, respectively) and physician referral (ACC for multivariate and univariate models were 0.68 and 0.63, respectively). Using McNemar's test, a significant difference was observed between the results of univariate and multivariate methods (p<0.05)

Table 2. Frequency (percentage) of re-admission and physician referral in seven time points

Response variable	Time 1	Time 2	Time 3	Time 4	Time 5	Time 6	Time 7	Total
Re-admission	8(6.7)	13(10.8)	18(15)	18(15)	15(12.5)	15(12.5)	13(10.8)	100(11.9)
Physician referral	31(25.8)	40(33.3)	48(40)	63(52.5)	39(32.5)	30(25)	51(42.5)	302(36)

Table 3. Results and formulas of univariate and multivariate generalized linear mixed-effects models assessing the frequency of re-admission and re-hospitalization

Response / Univariate models	independent variables	Estimate	Standard Error	p-value	Odds Ratio	CI 95%	
re-admission	group[1]	-2.038	1.088	0.0637	0.130	0.015	0.889
	time[2]	0.069	0.098	0.496	1.068	0.880	1.298
	time*group[3]	0.095	0.168	0.569	1.099	0.788	1.535
	RI[4]	3.662	0.837	<0.001	-	-	-
	ICC[5]	0.998	0.0002	<0.001	-	-	-
The formula	Re-admission= -2.038*group+0.069*time+0.095*group*time						
Referral	group[1]	-0.941	0.348	0.007	1.007	0.195	0.777
	time[2]	-0.034	0.513	0.506	1.658	0.873	1.069
	time*group[3]	0.159	0.074	0.034	1.034	1.012	1.359
	RI[4]	0.461	0.127	<0.001	-	-	-
	ICC[5]	0.537	0.142	<0.001	-	-	-
The formula	physician referral= -0.941*group-0.034*time+0.159*group*time						
Joint model							
re-admission	group[1]	-1.884	0.948	0.049	0.151	0.023	0.995
	time[2]	0.374	0.092	<0.001	1.453	1.177	1.700
	time*group[3]	0.210	0.167	0.211	1.233	0.886	1.721
	RI[4]	1.043	0.165	<0.001	-	-	-
	ICC[5]	0.996	0.002	<0.001	-	-	-
The formula	Re-admission= -1.884*group+0.374*time+0.210*group*time						
Referral	group[1]	-1.041	0.401	0.010	0.353	0.159	0.781
	time[2]	-0.046	0.055	0.408	0.955	0.855	1.066
	time*group[3]	0.189	0.080	0.020	1.208	1.029	1.416
	RI[4]	0.785	0.436	0.074	-	-	-
	ICC[5]	0.821	0.071	<0.001	-	-	-
correlation		0.905	0.257	<0.001	-	-	-
The formula	physician referral= -1.041*group-0.046*time+0.189*group*time						

[1](group=1 is the treatment and group=0 is the control)
[2]The continuous independent variable shows the passage of time
[3]The interaction between time and group which compares the development of response variable over time in the two groups
[4]Random Intercept variance
[5]The intraclass correlation caused by the repeated measurements over time

Table 4. Sensitivity, specificity, and accuracy of univariate and multivariate models in each time point and total

Univariate Models		Time 1	Time 2	Time 3	Time 4	Time 5	Time 6	Time 7	Total
re-admission	SE	0.79	0.96	0.97	0.98	0.85	0.76	0.74	0.87
	SP	0.87	0.84	0.66	0.72	1	1	1	0.89
	ACC	0.94	0.98	0.95	0.97	0.97	0.96	0.98	0.87
referral to doctor	SE	0.47	0.50	0.88	1	0.13	0	0.89	0.64
	SP	0.83	0.57	0.37	0.07	0.87	1	0.84	0.61
	ACC	0.86	0.95	0.83	0.91	0.89	0.91	0.97	0.63
Multivariate									
re-admission	SE	0.94	0.99	0.99	0.99	0.94	0.92	0.65	0.92
	SP	0.75	0.76	0.55	0.61	0..67	0.86	1	0.76
	ACC	0.91	0.98	0.88	0.96	0.95	0.96	0.95	0.90
referral to doctor	SE	0.57	0.75	0.95	0.96	0.73	0.10	0.84	0.80
	SP	0.80	0.57	0.37	0.15	0.53	1	1	0.47
	ACC	0.93	0.98	0.97	0.96	0.92	0.96	0.98	0.68

DISCUSSION

The result of this study showed that with the passage of time (weekly) after the discharge, there was a significant increases in the rate of re-admission in patients in the control group, while there was no significant increase in re-hospitalization. There was no statistical evidence showing a significant difference between the rates of re-admission over time between the treatment and control groups. In other words, the patients in both groups of treatment and control experienced a considerable increase in the odds ratio of re-admission over time, while it was only significant in the control group. Re-admission was more probable in the control group, as compared with the treatment group at the baseline and it was significant. In fact, a statistically significant difference in re-admission rate was found between the two groups immediately after the discharge, but such a difference was not observed over time. In contrast to re-admission, with a unit increase in time, the odds ratio of re-hospitalization significantly increased in the treatment group, as compared with the control group. This study showed an outperformance of multivariate approach to the univariate models. Several tools and indices can reveal better estimates made by multivariate approaches such as smaller standard errors of the estimated coefficients, and higher sensitivity, specificity, and accuracy in binary predictions. Longitudinal response variables have been assessed by lots of authors in recent years and generalized linear mixed-effects models have been the most common approaches used for dealing with this kind of data. Multivariate approaches provide detailed information about the data that are ignored by univariate approaches. The association between response variables is considered in multivariate analysis approach and it causes a smaller standard error in estimated coefficients, resulting in the true significance of the effects [19, 20]. Evaluating several response variables, Fieus et al. used random effects models where a joint distribution for the random effects joined separate sub-models [21]. Analyzing a developmental toxicity study of ethylene glycol in mice, Lin et al. used GLMMs to model clustered continuous and binary response variables jointly [22]. Multivariate (joint) and univariate statistical approaches has been evaluated and compared in several areas of medical research. Comparing dominance univariate and multivariate analysis, Azen and Budescu suggested utilizing multivariate approaches where the association between response variables has to be taken into account [23]. In a comparison and computational survey of various univariate and multivariate learning curve models, Badiru showed that the bivariate model provided a slightly better fit than the univariate model. Moreover, bivariate model provided more detailed information about the data [24]. Comparing multivariate and univariate GARCH models to forecast portfolio value-at-risk, Santos et al. concluded that the multivariate approach performs better than univariate approach [25]. McGuire et al. compared univariate and multivariate linkage analysis of traits related to hypertension. Taking into consideration the correlation between phenotypes, they showed that multivariate linkage analysis was better able to detect chromosomal regions while univariate linkage analysis only detected one gene [26]. Thorp used longitudinal joint and univariate mixed-effects models to assess metabolic syndrome data where multiple outcome variables were assessed using several predictors. He found that multivariate model was able to deal with the same questions addressed by the univariate model. Also, it answered additional important questions about the association between the evolutions of response variables, as well as the evolution of the associations. He showed that the association between the responses reduced the standard errors in estimations [27]. Davis et al. conducted a study on 125 patients hospitalized for heart failure. The study showed non-significant association between re-admission rates and developing heart failure knowledge within 30 days after the discharge [28]. In another study, Feltner et al. conducted a study on adults hospitalized with heart failure, and none of them neither tell monitoring nor primarily educational interventions reduced re-admission or mortality rates [29]. McHugh et al. showed that educational programs are not significantly associated with re-admission among patients with heart failure [30]. To assess the effects of teach-back method on reducing the rates of re-admission, White et al. conducted a study and found that long term education reduces re-admission rates compar to short-term teaching. However, as demonstrated, the correctly answered heart failure questions were not associated with a reduction in hospital re-admission rates [31]. In a randomized controlled clinical trial, Riegel et al. provided chronic heart failure patients with peer support, resulting in no significant association between education and re-admission rates [32]. The heart failure Adherence and Retention Randomized Behavioral Trial (HART) was conducted to assess the effects of an enhanced educational intervention along with self-management counselling. The study concluded that re-admission was not affected by the educational program [33]. In a multicenter, randomized, controlled trial, which was conducted based on the Coordinating Study Evaluating Outcomes of Advising and Counseling in Heart Failure (COACH), moderate and intensive disease management did not reduce the rates of death and re-admission [34]. A systematic review assessing the impact of social factors on risk of re-admission or mortality in pneumonia and heart failure patients showed that interventional training programs did not reduce the rates of re-admission in heart failure patients [35]. In contrast to the results of our study, in a research conducted by Peter et al., the understanding of patients' disease significantly improved and there was also a considerable reduction in re-admission rates [36]. In a randomized, controlled trial which was conducted on 223 systolic heart failure patients, Koelling et al. showed that with the addition of an hour, nurse educator–delivered teaching session at the time of hospital discharge reduced the cost of care in patients with systolic heart failure caused by re-admission; moreover, the clinical outcomes improved [37]. Rich et al. found that general trainings on HF by a registered nurse could reduce the number of all-cause re-admissions of elderly patients with congestive heart failure [38]. Collins et al. carried out a study to find out whether hospital admission was necessarily effective for heart failure patients. It revealed that the training and arranging of outpatient follow-ups were the two main tasks which were significantly associated with a decrease in re-admission [39]. Krumholz et al. introduced transition from inpatient to outpatient care, and concluded that the patient education and the admission thresholds were the important factors affecting re-admission on heart failure patients [40]. Another study by Wahba et al. revealed that an increase in education level was affective in decreasing the frequency of re-admission in heart failure patients within 30 days of discharge [41]. LO Hansen et al. conducted a study to evaluate physician referral rate. In this systematic review, 43 article published on pre-discharge and post-discharge intervention including follow-ups by telephone calls were reviewed and it did not show and association between intervention and physician referral.[42]

"The authors declare no conflict of interest"

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