

Relation between Hemoconcentration Status and Readmission Plus Mortality Rate Among Iranian Individuals with Decompensated Heart Failure

Abstract

Background: Hemoconcentration (HC) has been suggested to be a useful biomarker for determination of optimum diuretic therapy in acute heart failure (HF), but role of this factor in rehospitalization and death was still controversial. In this study, we aimed to define relation between HC and readmission and mortality rate among Iranian patients with acute HF. **Methods:** This was a prospective cohort study done from March 2017 to March 2018 using data of a HF section of Persian Registry Of cardiovascular diseases. From a total number of 390 registered HF individuals aged 18 years or older, 69 ones showed alterations in hemoglobin (Hb) levels. Hb levels were measured at admission and discharge time. HC was defined as any increased level in Hb during hospitalization. The relation of HC with readmission and death rate was done using multiple logistic regression and Cox proportional hazard model, respectively. **Results:** The mean age of study population was 70.5 ± 11.9 years with the dominant percentage of male participants (66.9%). Patients showing HC during admission did not reveal any significant decreased likelihood of rehospitalization compared to negative ones. In comparison to HC negative patients, those showing increments in Hb levels had a borderline significant lower likelihood of mortality (hazard ratio: 0.82, 95% confidence interval, CI = 0.07–1.18, $P = 0.08$). **Conclusions:** Our data suggested that HC was associated marginally with reduced mortality rate 6 months post HF attack and could be utilized as a useful biomarker for risk stratification of HF patients. Several prospective longitudinal population-based studies are necessary proving these associations.

Keywords: Anemia, heart failure, hemoglobins, hospitalization, patient admission

Introduction

One of the most common cardiac disorders accounts for 400,000 new cases and 2.6 million hospitalization per year with 6-year mortality of 80 and 65% in males and females, respectively is heart failure (HF).^[1,2] Its prevalence has estimated to be 0.5–12% in different nations.^[3-5] This entity plays role in 20% of hospitalizations in individuals aged at least 65 years plus approximate mortality rate of 55000 subjects in each year.^[6] Decreased quality of life and inducing great economic burden caused by this disease is inevitable.^[7,8] For instance, \$ 17.8 billion was spent for total HF care and treatment.^[6] Fluid retention leading to decompensation is one of the most common disabling symptom mostly observed in these patients. However, it was reported that some individuals would not experience extra fluid signs at all.^[9] Management of

this fluid retention due to declined heart pump function remains the cornerstone of decompensated HF therapy.^[9] Till today, diuretic therapy is one of the most usual decongested modality routinely used in health care settings, but optimum dosages leading to successful symptoms relief and decreased readmission rates required to be more investigated.^[10,11] Recently, hemoconcentration (HC) was introduced as a potential biomarker indicating the balance between intravascular volume reduction and capillary refill rate. This surrogate marker has been found to have associations with prediction of hospital readmission and mortality rates among HF patients.^[12] Multiple studies showed that HC was associated with lower death and readmission rates after HF occurrence.^[13,14] On the contrary, Davila *et al.* revealed that while mortality was lower in patients suffering from HF in univariate analysis,

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this relation became insignificant in multivariable adjusted models.^[15]

In addition to inconsistent results of studies and different definitions of HC, in this article we aimed evaluating the relation of HC on readmission on mortality rates among Iranian individuals referring with acute decompensated HF.

Methods

This was a prospective cohort study done from March 2017 to March 2018 using data of a HF section of Persian Registry Of cardiovascular diseases.^[16] All patients aged at least 18 years with acute decompensated HF confirmed by history and physical examinations, ejection fraction (EF) of less than 40% showed by echocardiography and past history of HF drug treatment especially with diuretics who was willing for participation in our study was recruited. Any histories of gastrointestinal bleeding or transfusion of blood components during 1 month prior to hospitalization date was defined as exclusion criteria. Two outcome variables including rehospitalization (yes/no) and death (yes/no) within 6 months after primary admission for HF attack was defined as our main study objectives. Other variables in this study were assessed including demographic ones (age (year) and gender (male/female)), anthropometric indices (body mass index (BMI) (kg/m^2)), past medical histories (hypertension (HTN) (yes/no), diabetes mellitus (DM) (yes/no), chronic obstructive pulmonary disease (COPD) (yes/no), renal problems (yes/no), ischemic heart disease (yes/no) and myocardial infarction (MI) (yes/no)), blood pressure indices (systolic blood pressure (SBP) (mmHg), diastolic blood pressure (DBP) (mmHg)) and laboratory profiles including hemoglobin (Hb) (g/dl), blood urea nitrogen (BUN) (mg/dl) and creatinine (Cr) (mg/dl). Other variables data except laboratory profiles were gathered only at admission time. Laboratory profiles were measured twice at the time of hospitalization and discharge date. Main exposure variable in this study was HC defined as any increased level of Hb from baseline to discharge date. Any individuals with an increase/decline in level of Hb from baseline to discharge date were considered as a positive or negative case of HC, respectively.

All participants were informed about the project from the start to the end date and any probable questions about the study were answered by the coordinator. Finally, a written consent form was signed by each individual. This study was approved by ethical committee of Isfahan University of Medical Sciences (No. 397038).

Statistical analysis

Categorical and continuous variables were reported as number (percentage) and mean \pm standard deviation (SD), respectively. Independent *t*-test and Chi-square test were used for comparison of continuous and categorical variables between patients with positive/negative HC, respectively. Relationship between HC and rehospitalization was

assessed via logistic regression. Confounders entered in final logistic regression included age, gender, and histories of ischemic heart disease, diabetes mellitus, hypertension, and renal problems.

We estimated hazard ratio of mortality using Cox proportional hazard model. The time variable used in this model was follow-up duration defined as the date of primary admission in hospital for HF until death date or otherwise a 6-month follow-up duration. After running a crude Cox regression model, HC variable was entered in a multiple Cox proportional hazard model adjusted for known confounders including age, sex, ischemic heart disease history, diabetes mellitus history, hypertension history, and renal problems history. Furthermore, relation between variables in baseline and discharge date according to HC status was done with paired *t*-test. All analyses were done with Statistical Package for Social Sciences (SPSS Inc., version 23.0, Chicago, IL, USA) and *P* values <0.05 were considered statistically significant.

Results

Among the total of 390 study participants, 260 patients (66.9%) were male. Due to incompleteness of discharge Hb for most of our samples HC predefined status was observed just for 69 patients (38 and 31 in negative and positive group, respectively). Baseline characteristics of study population according to HC status are presented in Table 1. HC positive individuals had significantly higher and lower BMI and Hb means compared to participants not showing any increments in Hb status ($28.6 \pm 4.5 \text{ kg}/\text{m}^2$ vs. $25 \pm 3.8 \text{ kg}/\text{m}^2$, $P = 0.01$ and $10.6 \pm 2.2 \text{ g}/\text{dl}$ vs. $13 \pm 2.2 \text{ g}/\text{dl}$, $P < 0.001$, respectively).

Table 2 provides information about SBP, DBP, Hb, BUN, and Cr means based on HC status. Although SBP and DBP declined significantly during hospitalization in total study population, this decreasing pattern was just remarkable in HC negative subgroups. In terms of Hb status, in spite of incremental alteration in all participants ($P = 0.001$), subjects with positive and negative HC status showed increasing and declining mean from the date of admission to discharge time. BUN and Cr raised and reduced significantly during hospitalization days, respectively ($P < 0.001$), but subgroup analysis failed to prove any significant relation.

Rehospitalization was occurred in 65 (16.7%) out of 390 patients (HC positive: 3 (9.7%) and HC negative: 6 (15.8%), $P = 0.45$). Data on odds ratio of readmission according to HC status are presented in Table 3. According to univariable logistic regression, in comparison to patients with negative HC during hospitalization, those with positive HC had a 42% lower risk of rehospitalization (odds ratio, OR: 0.58, 95% confidence interval, CI = 0.13–0.2.61, $P = 0.47$). After adjustment of all potential confounders, relationship was diluted (OR: 0.64, 95% CI = 0.14–3.03, $P = 0.57$). However, these relationships were not significant.

Table 1: Baseline characteristics of study participants according to hemoconcentration status

	Total (N=390)	Negative HC (N=38)	Positive HC (N=31)	P
Age (years)	70.5±11.9	71.0±12.1	72.1±10.5	0.70*
Gender (male)	261 (66.9)	26 (68.4)	24 (77.4)	0.40**
BMI (kg/m ²)	26.7±4.8	25.0±3.8	28.6±4.5	0.01*
SBP (mmHg)	132.8±28.2	125.1±22.5	131.7±27.1	0.27*
DBP (mmHg)	82.2±16.5	78.4±13.3	80.1±15.0	0.61*
Hb (g/dl)	13.2±4.2	13.0±2.2	10.6±2.2	<0.001*
BUN (mg/dl)	27.6±17.1	39.6±28.6	37.3±27.2	0.76*
Cr (mg/dl)	1.6±1.2	1.8±1.3	2.3±1.9	0.23*
Follow-up duration (days)	245.8±122.5	219.0±130.2	272.6±110.6	0.13*
Positive ischemic heart disease	318 (82.4)	29 (78.4)	20 (66.7)	0.28**
Positive COPD	40 (10.3)	5 (13.2)	6 (19.4)	0.48**
Positive renal diseases	96 (24.8)	9 (23.7)	11 (35.5)	0.28**
Positive hypertension	254 (65.6)	27 (71.1)	19 (61.3)	0.39**
Positive diabetes mellitus	184 (47.2)	21 (55.3)	17 (54.8)	0.97**
Positive myocardial infarction	126 (32.6)	8 (21.1)	8 (25.8)	0.64**
Readmission	65 (16.7)	3 (9.7)	6 (15.8)	0.45**
Death	62 (15.9)	27 (71.1)	24 (77.4)	0.54**

*P values are obtained from Independent T-test. **P values are obtained from Chi-square Test. BMI=Body mass index, SBP=Systolic blood pressure, DBP=Diastolic blood pressure, Hb=Hemoglobin, BUN=Blood urea nitrogen, Cr=Creatinine, COPD=Chronic obstructive pulmonary diseases

Table 2: Comparison of variables status between baseline and discharge time in study population according to hemoconcentration status

Variable	Baseline	Discharge	P*	
SBP (mmHg)	Total	132.9±28.1	117.3±21.6	<0.001
	Negative HC	127.4±20.9	112.9±16.9	0.002
	Positive HC	131.7±27.1	123.2±25.7	0.06
DBP (mmHg)	Total	82.2±16.6	73.4±12.4	0.001
	Negative HC	79.1±13.2	70.8±11.5	0.01
	Positive HC	80.1±14.5	74.8±15.1	0.08
Hb (g/dl)	Total	11.9±2.5	12.1±3.6	0.001
	Negative HC	13.0±2.2	11.7±1.9	<0.001
	Positive HC	10.6±2.2	13.0±4.5	0.001
BUN (mg/dl)	Total	31.9±20.2	34.3±18.8	<0.001
	Negative HC	38.7±29.2	33.1±14.9	0.31
	Positive HC	41.5±29.6	45.7±29.7	0.32
Cr (mg/dl)	Total	1.8±1.5	1.7±1.2	<0.001
	Negative HC	1.8±1.3	1.6±0.8	0.10
	Positive HC	2.4±2.0	2.3±1.9	0.12

*Quantitative data are presented as mean±standard deviation and compared by Paired T-test. SBP=Systolic blood pressure, HC=Hemoconcentration, DBP=Diastolic blood pressure, Hb=Hemoglobin, BUN=Blood urea nitrogen, Cr=Creatinine

Among 390 patients, 62 (15.9%) deceased after 6-month follow-up after primary admission for HF. Number (%) of deaths in positive and negative HC group was 11 (28.9) and 7 (22.6), respectively ($P = 0.54$). We assessed relationship between mortality and HC using Cox proportional hazard model, as presented in Table 4. As shown, HC reduced likelihood of 6-months mortality to 63% and 72% according to crude and adjusted models, respectively. Although there was not a significant relationship in crude

model ($P = 0.14$), we reached to a borderline significant relationship after adjustment for age, sex, ischemic heart disease history, diabetes mellitus history, hypertension history, and renal problems history (HR: 0.82, 95% CI = 0.07-1.18, $P = 0.08$).

Discussion

This study was conducted in order to find the relation between HC status and readmission, and mortality rate among Iranian adults suffering from decompensated HF. Since symptom relief is one of the most common treatment strategies and HC has been found to be a potential marker in decongested therapy and its beneficial effect in reducing readmission and death rate has been announced, measurement of this biomarker during hospitalization could effectively decline HF management expenses and increased patients' quality of life. Our data failed to prove any significant relations in terms of rehospitalization according to HC status. However, individuals who experienced incremental Hb levels had a borderline 72% decreased likelihood of mortality in comparison to patients did not show any alterations in Hb means. Several studies were in agreement with our outcomes.^[12,15,17] Davila *et al.* recruited 295 individuals with acute decompensated HF in their research. They measured Hb levels both at the time of admission and discharge. Their findings showed that HC was associated with decreased death rate (HR: 0.53, 95% CI = 0.29–0.96), but in adjusted model the result failed to be remained significant (HR: 0.78, 95% CI = 0.43–1.44, $P = 0.44$).^[15] Data analysis of 845 HF patients failed to prove any improvement in death rate among HC individuals, specifically during early hospitalization

Table 3: Odds ratio of rehospitalization according to hemoconcentration status using logistic regression

	Hemoconcentration negative	Hemoconcentration positive	P
Crude	1.00	0.46 (0.13-2.50)	0.45
Model 1	1.00	0.58 (0.13-2.61)	0.47
Model 2	1.00	0.64 (0.14-3.03)	0.57

Model 1: adjustment for age and sex

Model 2: adjustment for age, sex, ischemic heart disease history, diabetes mellitus history, hypertension history, and renal problems history

Table 4: Hazard ratio of mortality according to hemoconcentration status using Cox proportional hazard

	Hemoconcentration negative	Hemoconcentration positive	P
Crude	1.00	0.37 (0.10-1.43)	0.14
Model 1	1.00	0.30 (0.07-1.20)	0.08
Model 2	1.00	0.28 (0.07-1.18)	0.08

Model 1: adjustment for age and sex

Model 2: adjustment for age, sex, ischemic heart disease history, diabetes mellitus history, hypertension history, and renal problems history

(HR: 1.0, 95% CI = 0.80–1.3, $P = 0.93$).^[17] Although HC had been found to be associated with lower mortality in Darawsha and colleagues' study, they found that congestion itself was related more frequently with mortality rates independent of HC and no correlation was existed between congestion score and HC.^[12]

On the contrary, multiple studies revealed the inverse relations.^[9,11,18-20] Data analysis of 1180 and 1776 patients in two randomized double blinded prospective studies demonstrated that 2-month rehospitalization was less frequently observed in individuals showing HC plus good diuretic response.^[18] Another study on 336 HF persons with EF $\leq 30\%$ revealed that while HC defining as any increased level of Hb or hematocrit (Hct) or plasma protein from baseline to discharge time was associated with worsening of renal function, 6-month mortality had been significantly lower than subjects not showing HC.^[19] A total of 102 individuals admitted for acute decompensated HF were recruited for Fujita *et al.*'s study. Their Hb levels were retrospectively collected before hospitalization, on admission, 3 days posthospitalization and at discharge time and were further categorized to hemodilution (HD) and HC group based on their alterations in Hb levels. Their analyses suggested that HC individuals had been rehospitalized less frequently compared to HD ones ($P < 0.001$).^[9] Furthermore, Zhou and colleagues enrolled 510 patients suffering from acute HF and measured Hct levels as a biomarker for defining HC status at admission and seventh day of hospitalization or discharge time. They further divided them according to Hct levels to HC, HD, and no

change (NC) group. Finally, they found that persons with HC had a lower likelihood of death compared to HD (HR: 0.39, 95% CI = 0.24–0.63) and NC ones (HR: 0.54, 95% CI = 0.33–0.88).^[11] The other study on 2357 enrolled acute HF patients in order to calculate all-cause mortality and readmission rate suggested that obtaining HC during hospitalization period was associated with lower occurrence of adverse clinical events (HR: 0.67, 95% CI = 0.56–0.79, $P < 0.001$).^[20] One study done over 1969 individuals referring with acute HF plus mild to moderate kidney dysfunction. They assessed Hb during the first 4 days and on the 7th day of admission. Evaluating the relation between HC and 6-month all-cause mortality rate showed that Hb absolute changes predicted better clinical outcomes among HC subjects (HR: 0.66, 95% CI = 0.51–0.86, $P = 0.002$).^[14]

Despite our findings in terms of mortality was insignificant, our outcomes were compatible with previous studies reporting a declining pattern. Although the exact pathophysiological mechanism for this association has not found yet, several theories have been postulated. The most important explanation could be due to the role of diuretics. By prescription of diuretics as the cornerstone of HF symptomatic therapy, patients showing increased level of Hb during hospitalization has been found to be taking optimum dosages of the agent and their excess extravascular fluid responsible for their symptoms would be drained appropriately; therefore, they are categorized as good therapy responders and would experience less mortality compared with persons failed to increase their Hb levels.

Predefined reasonable follow-up duration and endeavor to overcome all potential confounders were some strengths of our current study. However, this study was associated with some limitations. The cross-sectional design of the research was one of the main limitations disabling us from deducing any causality relation. Defining HC just on the basis of Hb status should have been taken into account for generalization of the findings especially in studies considering raised level of other biomarkers including Hct or plasma protein as HC definition. Hb was just measured during hospitalization period and the status of stability after discharge might affect our outcomes. Furthermore, our main exposure variable (HC) data were incomplete for a large part of our sample as a result of not registered discharge Hb for them which might affect our reportable outcomes. However, our findings were in line with other studies that done on large samples. Also, we could not run a Cox proportional hazard model for rehospitalization outcome variable due to not registered rehospitalization dates in data registry. Because of study implementation in just one city in Iran, our findings must be interpreted cautiously in other nations or even other places in desired country.

Conclusions

Our findings suggested that increasing Hb level during hospitalization among acute HF patients was associated

with borderline reduced mortality rate and this biomarker could be effective in determining optimum diuretic therapy and decreasing oral dosages after discharge in addition to be used as an independent factor for risk stratification of patients referring with decompensated HF. Several randomized double-blinded and comprehensive prospective studies are required evaluating these possibilities for better health care strategies implementation.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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