Hematocrit change as a predictor of readmission for decompensated heart failure: a retrospective single centre study

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In patients with acute heart failure (AHF), hemoconcentration has been suggested as a surrogate for volume changes (AHF). However, literatures comparing the outcome of AHF patients that achieved hemoconcentration during hospitalization with those that do not are limited. The aim of this research is to see if achieving hemoconcentration prior to discharge is linked to a lower risk of re-admission in AHF patients. 124 patients hospitalized in the Cardiology Unit, University Malaya Medical Centre (UMMC) for AHF between November 2019 and November 2020 were enrolled. Information on patients' clinical characteristics, laboratory values and in-hospital treatments were collected through electronic medical record. At admission and discharge, the change in hematocrit (HCT) levels was calculated, and patients were stratified based on two quantiles of delta HCT, either discharged with hemoconcentration (ΔHCT >1.5%) or without hemoconcentration (ΔHCT $\leq$1.5%). The study's outcome was AHF readmission after a 90-day follow-up period. Readmission was significantly associated with ejection fraction (p = 0.032) and HCT change (p = 0.005). Consecutively, logistic regression performed revealed that patients with haemoconcentration were 78.3% less likely to be readmitted than those without haemoconcentration (OR = 0.217, p = 0.003, 95% CI = 0.078–0.605) and Patients with a lower ejection fraction have a threefold greater chance of being readmitted than those with a preserved ejection fraction (OR = 3.316, p = 0.022, 95% CI = 1.188–9.256). In conclusion, among patients hospitalized and discharged for AHF, those that (i) do not achieve haemoconcentration and (ii) patients with a reduced ejection fraction were more likely to be readmitted with acute heart failure. Therefore, optimising patients' haematocrit levels prior to discharge may potentially reduce rehospitalizations among heart failure patients.

Keywords

Heart failure; Haemoconcentration; Re-hospitalisations; Outcome; Decompensated

1. Introduction

Due to the disease's complex underlying pathophysiology, optimal volume management in acute heart failure patients is important but complicated. The main goal of decompensated heart failure is to eliminate additional intravascular and extravascular fluid, as well as alleviate congestive signs and symptoms [1].

The peptide hormone, brain natriuretic peptide (BNP), which is secreted primarily by ventricular myocytes in response to cardiac wall stretching and distension, is essential for volume homeostasis. Measurement of plasma brain natriuretic peptide had been proposed as marker of diagnosis of volume overload and prognostication in HF patients [2]. However, the test is costly and not readily available at each healthcare centre.

HCT measurement has been proposed as a suitable surrogate for volume status measurement because it is readily available and less costly than BNP [3]. Achievement of haemoconcentration in hospitalized AHF patients had been shown leading to better survival, compared to those that do not achieve haemoconcentration [3–5]. However, such data unfortunately remain scarce within most South-East Asian countries, such as Malaysia. As a result, the aim of this research is to see if achieving haemoconcentration prior to discharge is linked to a lower risk of re-admission in inpatient AHF patients.

2. Methodology

2.1 Study design

This is a cross-sectional analysis performed retrospectively in the Cardiology Unit of a single tertiary center, University Malaya Medical Centre (UMMC, Kuala Lumpur, Malaysia) from 1st November 2019 to 30th November 2020. Patient information on demographics, investigations (bloods and echocardiography) and medications were obtained through UMMC's Electronic Medical Record (EMR).

2.2 Study population

The target population consisted of all patients registered in MyHeart Failure (MyHF) UMMC Registry within the study duration. MyHF registry recorded 237 admissions to UMMC with a diagnosis of HF between 1st November 2019 and 30th November 2020. We used the first hospitalisation as the index hospitalisation for patients who had several hospitalizations in the registry. Patients with unrecorded admission and discharge HCT values, active bleeding or patients receiving inpatient iron or blood transfusion, end stage re-

nal disease (requiring erythropoietin and renal replacement therapy), and pass away during the index admission were excluded from analysis. Since excluding 113 patients who did not meet the inclusion criterion, a total of 124 patients were identified for the analyse. All patients gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the University Malaya Medical Centre Ethics Committee (20201126-9539).

2.3 Study end-point

Re-admission for AHF within 90 days post discharge.

2.4 Method for end-point identification

Phone calls and EMR assessment to identify patients who had re-admission for AHF within 90 days post discharge.

2.5 Data management

The difference in HCT(ΔHCT) between admission and discharge was used to divide the patients into two groups in this study [6]:

Haemoconcentration (ΔHCT >1.5%);

No Haemoconcentration (ΔHCT $\leq$1.5%).

Data on patient's demographics, investigations (bloods and echocardiography) and medications were obtained through UMMC's EMR.

Each patient's EMR record was then reviewed to see if they were readmitted again for acute HF within 90 days post discharge.

2.6 Statistical analysis

IBM SPSS Statistics for Windows Version 26 is used to conduct the analyses. Descriptive statistics were utilized for the variables. For categorical statistics, the results were presented as percentages and frequencies. Numerical data that is normally distributed is presented as mean and standard deviation, while numerical data that is not normally distributed is presented as interquartile range and median. The relation between the variables and readmission was investigated using Pearson's Chi-square test (SPSS IBM version 26) for independence. The researcher applied binomial logistic regression to find predictors of 90-day readmission owing to heart failure. If the univariate analysis p value was less than 0.25, predictors were included. All probability values will be two-sided, and statistical significance will be defined as a level of significance of less than 0.05 (p-value 0.05).

3. Results

3.1 Population characteristics

The baseline characteristics of the study population are shown in Table 1. The mean age of the participants in the research was 63.6 $\pm$ 12.7 years, more than half were male (58.9%), and majority were Malay of ethnicity (44.4%). Majority had comorbidities and exhibited signs of heart failure on physical examination upon admission, and a great number had reduced ejection fraction (63.7%). A small proportion of the patients were discharge with hemoconcentration

(28.2%), and 39.5% were readmitted for heart failure within an average duration of 34.1 $\pm$ 30.0 days.

3.2 Associations with heart failure readmission

Table 2 shows the association between patients' sociodemographic backgrounds, comorbidities and hematocrit changes with readmission for heart failure. Readmission and ejection fraction (p = 0.032) and hematocrit change (p = 0.005) showed statistically significant relationships in a Chi-square test (SPSS IBM version 26) for independence. Whereas no significant associations were found between admission and other variables.

3.3 Predictors for heart failure readmission

Each variable was subjected to univariate analysis, and a total of six variables with $p < 0.25$ were chosen to be included in the multivariate logistic regression model. To determine the impact of ejection fraction and hematocrit a change on the likelihood of readmission, a binomial logistic regression was used (Table 3). The logistic regression model was significant statistically, X^2 (9) = 27.977, p = 0.001. The model properly identified 74.2 percent of patients and explained 27.3 percent of the variation in readmission (NagelkerkeR2). Odds of readmission was 3.316 greater for patients with decreased ejection fraction, in contrast to those with preserved ejection fraction (p = 0.022, 95% CI = 1.188–9.256), while patients with hemoconcentration were 78.3% less likely to be readmitted than those with hemodilution or no change in hematocrit levels (p = 0.003, 95% CI = 0.078–0.605).

4. Discussions

Heart failure (HF) is a clinical symptom that occurs at the conclusion of most heart diseases. The frequency of HF ranges from 3 to 20 per 1000 population, and it can be as high as 100 per 1000 population in those over the age of 65 [7]. Heart failure can be classified into 3 classes; (i) heart failure with preserve ejection fraction (HFpEF) EF $\geq$50%, (ii) HF with midrange ejection fraction EF 40–49% (HFmrEF), (iii) and Heart failure with reduced ejection fraction, EF <40% (HFrEF) [8].

AHF is described as the onset of new or worsening HF symptoms in a short period of time [9]. Most of time, AHF patients require recurrent hospitalization and urgent therapy to relive their symptoms. In Malaysia, AHF accounts for 6% to 10% of all acute hospital admissions [10].

HF also carries poor prognosis. A landmark registry in United States of America (USA), OPTIMIZE-HF showed that within 3 months of an index HF hospitalization, there is 30% readmission rate and an associated 10% mortality rate [11]. 1-year mortality rate for a patient that been admitted for AHF is around 30% [12].

From a financial perspective, management of HF patients is also associated with increased healthcare expenditures. In 2012, the global economic impact of Heart failure was projected to be $108 billion a year [13]. In Malaysia, the total cost of heart failure was projected to be $USD 194 million (MYR

Table 1. Baseline characteristics.

Variable	n (%)	Mean (SD)	Median (IQR)
Sociodemographic background			
Age (years)		63.63 (12.707)	
Gender			
Male	73 (58.9)		
Female	51 (41.1)		
Ethnicity			
Malay	55 (44.4)		
Chinese	33 (26.6)		
Indian	35 (28.2)		
Others	1 (0.8)		
Medical background			
Type 2 diabetes			
No	43 (34.7)		
Yes	81 (65.3)		
Hypertension			
No	27 (21.8)		
Yes	97 (78.2)		
Chronic kidney disease			
No	21 (16.9)		
Yes	103 (83.1)		
Dyslipidemia			
No	36 (29.0)		
Yes	88 (71.0)		
Ischemic heart disease			
No	50 (40.3)		
Yes	74 (59.7)		
Atrial fibrillation			
No	95 (76.6)		
Yes	29 (23.4)		
Smoker			
No	103 (83.1)		
Yes	21 (16.1)		
Physical examination on admission			
Raise jugular venous pressure			
No	27 (21.8)		
Yes	97 (78.2)		
Crept			
No	7 (5.6)		
Yes	117 (94.4)		
Edema			
No	30 (24.2)		
Yes	94 (75.8)		
Laboratory values on admission			
Hct (%)		40.00 (6.144)	
Hb (g/dL)		12.513 (2.0271)	
Urea (mmol/L)			8.900 (6.2)
Creatinine (μmol/L)			111.50 (78)
Laboratory values on discharge			
Hct (%)		39.56 (10.632)	
Hb (g/dL)		12.032 (1.9910)	
Urea (mmol/L)			10.100 (7.6)
Creatinine (μmol/L)			103.00 (73)

Table 1. Continued.

Variable	n (%)	Mean (SD)	Median (IQR)
Sociodemographic background			
Discharge medication			
RAS blockade			
No	53 (42.7)		
Yes	71 (57.3)		
Beta blocker			
No	31 (25.0)		
Yes	93 (75.0)		
Aldosterone antagonist			
No	79 (63.7)		
Yes	45 (36.3)		
SGLT2 inhibitor			
No	27 (21.8)		
Yes	97 (78.2)		
Diuretic			
No	17 (13.7)		
Yes	107 (86.3)		
Hematocrit change			
ΔHCT >1.5%	35 (28.2)		
ΔHCT ≤1.5%	89 (71.8)		
Ejection fraction			
Preserved	30 (24.2)		
Midrange	15 (12.1)		
Reduced	79 (63.7)		
Readmission			
No	75 (60.5)		
Yes	49 (39.5)		
Duration of admission (days)			4.00 (5)
Duration to readmission (days)		34.10 (30.009)	

n, frequency; SD, standard deviation; IQR, interquartile range.

785 million), with direct and indirect expenses of \$USD 12 million (MYR 48.7 million), and \$USD 182 million (MYR 740 million) correspondingly, accounting for around 1.8 percent of total health spending [13].

AHF is caused by a variety of causes. The majority of patients hospitalised with AHF exhibit volume overload, according to data from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) [11] and Acute Decompensated Heart Failure Registry (ADHERE) registries [14].

The fluid flow within and outside the vessel maintains a dynamic balance under physiological circumstances. Haemoconcentration occurs when intravascular fluid is lost quicker than it can be replenished by extravascular fluid. Evidence suggested that measurement of BNP in HF patients reflected the intravascular volume status and also disease severity. A study been done by Pimenta et al. [15] in 2010 to investigate the relation of volume status, measured by thoracic fluid content (TFC), with regards to BNP level. The study showed that those with higher TFC value (volume overload) had higher BNP level (BNP >1000 pg/mL). Statistically, multivariable linear regression study indicated that TFC is a significant de-

terminant of the BNP level (β = 0.043, 95% CI 0.024–0.062, $p < 0.001$). Aside from that, the study discovered that severe systolic dysfunction is a robust predictor of BNP levels ($p = 0.001$) (β = 0.831, 95% CI 0.449–1.212). According to the BNP Consensus Panel, higher BNP levels are inversely proportionate to cardiac output and are strongly connected with intraventricular pressure, pulmonary pressure, prognosis, and New York Heart Association (NYHA) score [16].

Aside from BNP, pulmonary artery catheterization measurements (central venous pressure, pulmonary capillary wedge pressure) [17] and tracer methods (i.e., I131-tagged albumin) can be employed to assess intravascular volume status [18]. However, these procedures are frequently invasive, time-consuming, and costly, and they are not easily available in every healthcare facility.

Haemoconcentration, defined as a rise in haemoglobin (Hb), HCT, or plasma albumin, has been proposed as a suitable surrogate for assessing volume status changes [3, 4]. Studies showed that achievement of haemoconcentration is linked with better result.

Testani et al. [3] analysed the landmark ESCAPE study [19] and found that patients with haemoconcentration got

Table 2. Association of sociodemography, comorbidity and haematocrit changes with readmission.

Variable	Readmission		x^2 statistic (df)[a]	p-value[a]
	No (n = 75)	Yes (n = 49)		
Gender				
Male	45 (60.0)	28 (57.1)	0.10 (1)	0.752
Female	30 (40.0)	21 (42.9)		
Ethnicity				
Malay	38 (50.7)	17 (34.7)		
Chinese	18 (24.0)	15 (30.6)	4.046 (3)	0.229
Indian	18 (24.0)	17 (34.7)		
Others	1 (1.3)	0 (0.0)		
Type 2 diabetes				
No	23 (30.7)	20 (40.8)	1.35 (1)	0.246
Yes	52 (69.3)	29 (59.2)		
Hypertension				
No	14 (18.7)	13 (26.5)	1.08 (1)	0.300
Yes	61 (81.3)	36 (73.5)		
Chronic kidney disease (eGFR <60)				
No	12 (16.0)	9 (18.4)	0.12 (1)	0.731
Yes	63 (84.0)	40 (81.6)		
Dyslipidemia				
No	20 (26.7)	16 (32.7)	0.52 (1)	0.473
Yes	55 (73.3)	33 (67.3)		
Smoker				
No	63 (84.0)	40 (83.3)	0.01 (1)	0.922
Yes	12 (16.0)	8 (16.7)		
Ischemic heart disease				
No	32 (42.7)	18 (36.7)	0.433 (1)	0.510
Yes	43 (57.3)	31 (63.3)		
Atrial fibrillation				
No	57 (76.0)	38 (77.6)	0.040 (1)	0.842
Yes	18 (24.0)	11 (22.4)		
RAS blockade				
No	28 (37.3)	25 (51.0)	2.27 (1)	0.132
Yes	47 (62.7)	24 (49.0)		
Beta blocker				
No	17 (22.7)	14 (28.6)	0.55 (1)	0.458
Yes	58 (77.3)	35 (71.4)		
Aldosterone antagonist				
No	50 (66.7)	29 (59.2)	0.718 (1)	0.397
Yes	25 (33.3)	20 (40.8)		
SGLT2 inhibitor				
No	61 (81.3)	36 (73.5)	1.076 (1)	0.300
Yes	14 (18.7)	13 (26.5)		
Diuretic				
No	7 (9.3)	10 (20.4)	3.073 (1)	0.080
Yes	68 (90.7)	39 (79.6)		
Hematocrit change				
ΔHCT >1.5%	28 (37.3)	7 (14.3)	7.771 (1)	*0.005
ΔHCT ≤1.5%	47 (62.7)	42 (85.7)		
Ejection fraction				
Preserved	22 (29.3)	8 (16.3)		
Midrange	12 (16.0)	3 (6.1)	6.90 (2)	*0.032
Reduced	41 (54.7)	38 (77.6)		

[a] Chi-square test for independence; * Association is significant at 0.05 level (2-sided).

n, frequency; df, degree of freedom.

Table 3. Predictors of readmission among heart failure patients.

Predictors	OR	95% CI	p-value
Ethnicity (ref. Malay)			
Chinese	2.299	0.815–6.484	0.116
Indian	1.719	0.639–4.623	0.283
Others	0.000	–	1.000
DM (ref. No DM)			
Yes	0.519	0.212–1.270	0.151
RAS blockade (ref. Not discharged with RAS Blockade)			
Yes	0.425	0.176–1.028	0.058
Diuretic (ref. Not discharged with diuretic)			
Yes	0.507	0.160–1.611	0.250
Ejection fraction (ref. Preserved EF)			
Midrange	0.732	0.140–3.820	0.711
Reduced	3.316	1.188–9.256	0.022*
Hematocrit change (ref. Without hemoconcentration)			
Hemoconcentration	0.217	0.07–0.605	0.003*

* Significant predictor at 0.05 level.

ref, reference; OR, odds ratio; CI, confidence interval.

larger doses of loop diuretics, lost more weight/fluid, and had bigger decreases in filling pressures ($p < 0.05$ for all), but at the risk of decreasing renal function (OR = 5.3, $p < 0.001$). They also discovered that people in the haemoconcentration group had a decreased 180-day death rate (HR = 0.31, $p = 0.013$).

Van der Meer et al. [4] found that an increase in Hb is linked to increase in HCT ($p < 0.01$), greater weight loss ($p < 0.01$), and improved 180-day survival ($p = 0.002$, 95% confidence interval: 0.51 to 0.86, hazard ratio: 0.66) [20]. However, they also discovered that this group of patients is at risk of deteriorating renal function ($p = 0.01$, percentage change in creatinine $+6.4 \pm 26$ vs. $+3.1 \pm 26$).

According to a study by Zhou et al. [6], Increased HCT during hospitalisation is related with a decreased risk of all-cause mortality compared to those who do not demonstrate an increase in HCT [$p < 0.001$, 95% confidence interval (CI) 0.24–0.63, hazard ratio (HR) 0.39]. They discovered that decreasing renal function did not differ substantially between the two groups ($p = 0.15$).

This present study has demonstrated that change in HCT and ejection fraction is strong predictors for readmission due to AHF among patients hospitalized with acute heart failure. We found that patients that do not achieve hemoconcentration prior to discharge had higher risk of readmission due to AHF, when compared to those that achieved hemoconcentration. This finding is consistent with previous studies showing patients hospitalized for HF that achieved hemoconcentration had more favorable outcome, when compared to those without hemoconcentration [3–6].

When compared to HFpEF, patients with HFrEF had a greater risk of readmission, but HFmrEF appeared to be a protective factor against readmission. Interestingly, previous data on readmission risk had shown conflicting results when taking EF as a predictor for readmission.

For example, Cheng et al. [21] discovered that in the HFrEF population, HF-specific readmissions were greater than in the HFpEF population, with 30.9% vs. 24.3% at 1 year respectively and 9.0% vs. 6.1% at 30 days ($p < 0.001$).

However, a metaanalysis by Altaie et al. [22] in the HFmrEF population found that the probability of an heart failure associated readmission was identical in HFmrEF compared to HFpEF or HFrEF. according to a recent research by Santas et al. [23], when compared to patients with HFrEF or HFpEF, patients with HFmrEF had a similar rehospitalization cost and a similar likelihood of recurring all-cause and heart failure-related admissions after an Acute heart failure stay.

In HFrEF patients, improvement in EF has been found to be a positive prognostic measure. Ghimire et al. [24] found that HF with recovery EF (HFrecEF), defined as EF improvement of $\geq 10\%$ on the follow-up echocardiagram, demonstrated lower rates per 1000 patient years of mortality (aHR 0.70 [0.62–0.79], adjusted hazard ratio, 106 vs. 164), cardiac transplantation or left ventricular assist device implantation (aHR 0.21 [0.10–0.45], 2 vs. 10), all-cause emergency room (ER) visits (aHR 0.88 [0.81–0.95], 569 vs. 799), and all-cause hospitalizations (aHR 0.87 [0.79–0.95], 300 vs. 428) compared to patients with persistent HFrEF.

Unlike all the results of landmark studies and guideline, we found that prescription of the standard medical therapies drugs, namely renin-angiotensin system (RAS) blockade [25], beta blocker (BB) [26], aldosterone antagonist [27] and diuretic [28], were not significantly associated with reduction in readmission. This might be described by the differences in study designs patients', concomitant medical therapy, and background. For example, the MERIT-HF study [26] investigated patients with chronic and stabile with LVEF ≤ 40 as opposed to all (HFrEF, HFpEF and HFmrEF) hospitalised acute decompensated HF patients in our study. Studies of Left Ventricular Dysfunction (SOLVD) Treatment Trial [25] on

the other hand, due to its strict exclusion criteria comprises only 6.4% patients with HFrEF compared to our study of 63.7%. Furthermore, we found sub-optimal prescribing rate especially in RAS blocker in our study patients. The low prescription rate in RAS blockade is also seen our Malaysian national cardiovascular database registry for ACS which shows RAS blockage prescription rate of only around 50% [29, 30]. The possible limiting factors would be hypotension, worsening kidney function or physician's cautions in prescribing RAS blockage in patients with impaired kidney function.

Time to event analysis results showed that those with haemoconcentration tend to be readmitted earlier after discharge, compared to those that did not achieve haemoconcentration, despite haemoconcentration is a protective factor from readmission. So far there is no comparable data available. We hypothesized that this is maybe because of other unmeasurable confounding factors, such as fluid restriction and also patient's compliance to medication. Further studies are needed to further determine this association.

5. Limitation

Our study has limitation that need to be emphasised. This research was a retrospective single-centred analysis, which may not give the full picture of all AHF admission. Furthermore, using HCT change as a substitute for direct measures of plasma volume to check for changes in volume status may be insufficiently precise. In example, compared to volume overload state in AHF which leads to low HCT level (haemodilution), HCT level also will be low in a case of gastrointestinal bleed, which in this situation, patient will be in volume depleted state. According to Van der Meer *et al.* [4] remaining congestion was seen in 41% of patients with haemoconcentration and 53% of patients without haemoconcentration. This demonstrates that despite haemoconcentration, a large number of patients have clinically persisting congestion. We were also unable to eliminate out any measured and unmeasured confounding variables that may have influenced the results. Compliance to medications, fluid and salt restrictions and achievement of optimum doses of guideline-recommended drugs were not taken into analysis. Finally, further additional relevant data to support the assessment of plasma volume such as serum albumin level, NYHA class status, clinical decongestion assessment at discharge and total net fluid balance were not available.

6. Conclusions

Our study found that haematocrit change is a reliable predictor for AHF readmission and potential therapeutic target in HF. Patients with AHF who achieve haemoconcentration before to release are less likely to be readmitted for AHF within 90 days. We also found that patients with reduced EF are more likely to be readmitted for AHF compared to other groups. Therefore, we recommend on practice of monitoring of the haematocrit level prior to discharge among all AHF patients. Those that do not achieve haemoconcen-

tration likely will benefit from higher dosage of diuretics and earlier follow up. We also recommend on active measures to improve patients' EF, either medically (optimize anti-failure as per GDMT) or invasively (percutaneous angiogram, left ventricle assist device) to improve overall outcome. Additional large-scale, prospective, randomised controlled trials are needed to validate and describe the link between short-term changes in HCT and prognosis, as well as to establish effective volume management techniques for AHF patients.

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