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Research Article

ESTIMATION OF PLASMA VOLUME IN PATIENTS PRESENTING WITH ACUTE DECOMPENSATED HEART FAILURE USING KAPLAN – HAKIM FORMULA AND CORRELATION OF PLASMA VOLUME SHIFT WITH OUTCOMES

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ABSTRACT

Objective: Simple and non-invasive methods are required to estimate the plasma volume expansion to assess the congestion status in heart failure patients. To determine the effectiveness of Kaplan–Hakim formula in the quantification of the plasma volume expansion in acute decompensated heart failure (ADHF) and the correlation of the outcome factors with plasma volume shift (PVS).

Methods: This prospective study included 384 participants diagnosed with ADHF. Newly diagnosed cases and patients receiving treatment for the past 6 months were included. Kaplan–Hakim formula was used to estimate the plasma volume. Duration of hospital stay, subsequent hospitalization for heart failure (HHF), cardiovascular disease mortality, and all-cause mortality rate at the end of follow-up time was also noted.

Results: Among the study participants, 88 patients (22.92%) had PVS <5%, while the remaining 88.5% of the patients had PVS more than or equal to 5%. A strong association between guideline-recommended dose of ACEi/ARBs, beta-blockers, and normalcy of plasma volume status ($p<0.001$) was found. The mean duration of stay, number of repeated hospitalization, the incidence of worsening renal function, CV mortality rate, and all-cause mortality rate were significantly lower in participants with PVS ≥5% in comparison to those who had PVS < 5%. Kaplan–Hakim formula is a more practical and easy way to measure volume status in patients with ADHF.

Conclusion: The use of RAAS antagonists and beta-blockers in their optimal dosage is associated with favorable plasma volume status in chronic HF patients.

Keywords: Kaplan–Hakim formula, Plasma volume shift, Acutede compensated heart failure, Worsening renal function.

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INTRODUCTION

Acute decompensated heart failure (ADHF) is a commonly reported health problem worldwide, with significant readmission rates and high mortality. The number of reported ADHF cases is on the rise due to improvements in health-care facility and increased longevity. The major causes for repeated hospitalization in patients with heart failure are due to the symptoms and signs of congestion [1]. Repeated hospitalization due to ADHF cause an increased burden to both the health-care facility and patients. Even though, the prognosis had gradually increased over the years in heart failure patients, still lacunae exist in the long-term treatment of heart failure patients. Quantifying the congestion and appropriate management remains the cornerstone in the management of ADHF patients [2].

Even though several different biomarkers and clinical score systems. Biological parameters and radio tracer indicator-dilution methods were available; the gold standard method in the assessment of congestion in heart failure patients is right heart catheterization. However, the procedure is invasive and requires a high standard of care in carrying out the procedure [3,4]. Therefore, an appropriate and easy tool is required for the detection of congestion.

Plasma volume expansion is one of the major pathophysiologic changes seen in ADHF. Plasma volume regulation control by the reninangiotensin aldosterone system is impaired, and sympathetic nervous system activation happens in heart failure patients [5]. Plasma volume expansion leads to an increase in body weight, edema, and other congestive symptoms. However, the lesser degree of plasma expansion often goes unnoticed. This is often seen as a missed opportunity to prevent hospitalization in ADHF.

In order to assess the congestion status in ADHF, plasma volume should be assessed using easy and non-invasive methods. Previous studies have estimated the predictive accuracy of different indices in estimating the plasma volume in heart failure patients [6-8]. This study was carried out with the objective to determine the effectiveness of Kaplan - Hakim formula in the quantification of plasma volume expansion in ADHF and the correlation of the outcome factors with plasma volume shift (PVS).

MATERIALS AND METHODS

Study participants and settings

This prospective follow-up was done in a tertiary health-care hospital between January 2020 and December 2020. Altogether, 384 ADHF patients were recruited for the study after obtaining consent as per guidelines and ethical clearance from the ethics committee. Patients with age above 18, who had been diagnosed with heart failure and were on standard treatment care for heart failure for at least 6 months, were included. All new heart failure cases with signs and symptoms and recurrent cases requiring urgent hospitalization and treatment were the study participants. Patients with valvular or congenital heart disease, chronic liver disease, nephrotic syndrome, advanced kidney disease, patients on hemodialysis, hemoglobinopathies, recent blood transfusions and any other diseases which are likely to impact hemoglobin and plasma volume status independent of cardiac function were excluded from the study.

Study variables

Baseline clinical variables and treatment history were noted for all patients. Patients were managed with standard treatment for ADHF during their hospital stay. Plasma volume status was calculated using Kaplan–Hakim formula on admission using following formula:

APV (in L) = (0.065 × Weight kg) × (1−HCT)

The PVS was calculated depending on the increase or decrease in the plasma volume from the ideal plasma volume. Duration of hospital stay, subsequent hospitalization for heart failure (HHF), cardiovascular disease mortality and all-cause mortality rate at the end of follow-up period (1 year) were also noted.

Statistical analysis

IBM SPSS 24.0 statistics for Windows software was used for data analysis. Continuous variables were expressed in the median with 25^{th}–75^{th} percentiles and nominal variables were expressed in percentage. Baseline characteristics and outcome parameters were compared between PVS <5% and ≥5%. Mann - Whitney test (Kruskalwallis test for 3 or more variables) was used to analyze parametric variables. Pearson's Chi-square test (or Fisher's exact test) was used to analyze non-parametric variables. $p<0.05$ was fixed for statistical significance.

RESULTS

Table 1 describes the clinical parameters of the study population. Study participants' mean age in years was 62±9 and males (72.6%) constituted majority of them. The mean value of left ventricular ejection fraction among the patients was 44±6%. Most of the patients had LVEF <50% (84%). The mean hemoglobin level of the study participants was 11.2±2.1 gm/dl and the mean weight in kg was 58.4±9.1.Diabetes mellitus was the most commonly seen comorbid condition (31%), followed by atrial fibrillation (22%). Most of the patients had been treated with ACEi/ARBs (82.81%) and beta-blockers (85.94%).

Table 2 describes the correlation of heart failure medication dosage with PVS. Study participants were divided into two groups (PVS <5% and PVS above or equal to 5%) to compare the outcomes. Outcome variables are also compared among those having PVS <0.

88 patients (22.9%) had reported PVS <5%, while the remaining 296 (88.5%) had PVS more than or equal to 5%. Only 6% of the study population reported PVS <0, signifying net plasma volume contraction. Analysis of the dosage of various HF medications with PVS showed a strong association between guideline-recommended dose of ACEi/ARBs, beta blockers, and normalcy of plasma volume status ($p<0.001$ for both ACEi/ARB and beta blockers).

Table 3 summarizes the correlation between PVS and outcome parameters. In patients with PVS <5% mean length of stay during index hospitalization (2.8±0.8 days) was significantly lower than in patients with PVS ≥5% (4.9±1.2 days, $p<0.001$). Hospitalizations for heart failure during one year follow-up also differed significantly in the two groups, the mean frequency of HHF per patient in PVS <5% group was 1.89±0.2 versus 2.62±0.5 in PVS ≥5% group ($p<0.001$). The incidence of worsening renal function (WRF) was significantly more in PVS <5% group (mean increase in creatinine [0.2±0.15 vs. −0.3±0.24] in PVS ≥5% group).

After the follow-up period of 1 year, a total of 36 deaths occurred, out of which only five deaths occurred during the index hospitalization. Among 36 deaths, five deaths were due to non-cardio-vascular causes. Both all-cause mortality (33 in PVS ≥5% vs. 3 in PVS <5%, $p=0.0352$)

Table 1: Baseline parameters of the study population

Parameter	n=384	PVS<5%, (n=88)	PVS≥5%, (n=296)
Age (years), mean±SD	62±9	57±3.4	63.5±4.8
Sex (%)			
Male	279 (72.66)	62	217
Female	105 (27.34)	26	79
Ejection fraction (%)			
<50	322 (83.85)	45	277
≥50	62 (16.15)	43	19
Weight (kg), mean±SD	58.4±9.1	51.2±4.1	60.5±6.2
Hemoglobin (gm/dL), mean±SD	11.2±2.1	10.2±0.9	11.5±1.6
Serum creatinine (mg/dL), mean±SD	1.2±0.3	1±0.15	1.26±0.28
Co-morbidity, n (%)			
DM	119 (31)	22	97
AF	84 (22)	38	46
CKD	46 (12)	6	40
COPD	27 (7)	13	14
CVA	15 (3.9)	5	10
PVA (mL)	3110 (1756–6210)	2190	3384
IPV (mL)	2307 (1660–4680)	2022	2392
PVS (%)	14.3 (−4.3–28.4)	1.90	17.99

AF: Atrial fibrillation, CKD: Chronic kidney disease, COPD: Chronic obstructive pulmonary disease, DM: Diabetes mellitus, CVA: Cerebrovascular accident, IPV: Inactivated poliovirus vaccine, PVA: Polyvinyl alcohol, SD: Standard deviation, PVS: Plasma volume shift

Table 2: Correlation of heart failure medications and dosage with plasma volume shift

Drug (%)	Dosage (%)	n (%)	PVS<5%	PVS≥5%	p
ACEi/ARB (82.81)	≥50 of recommended	40 (10.42)	36	4	<0.001
	<50 of recommended	278 (72.4)	44	234	
	Nil	66 (17.19)	8	58	
MRA (16.67)	≥50 of recommended	12 (3.13)	4	8	0.024
	<50 of recommended	52 (13.54)	19	33	
	Nil	320 (83.33)	65	255	
Beta blocker (85.94)	≥50 of recommended	56 (14.58)	44	12	<0.001
	<50 of recommended	274 (71.35)	41	233	
	Nil	54 (14.06)	3	51	
Diuretics (39.06)	≥50 of recommended	34 (8.85)	6	28	0.022
	<50 of recommended	116 (30.21)	37	79	
	Nil	234 (60.94)	45	189	

ACEi/ARB: Angiotensin-converting enzyme inhibitor/angiotensin receptor blockers, PVS: Plasma volume shift, MRA: Mineralocorticoid antagonists

Table 3: Correlation between plasma volume shift and outcome parameters

Parameter	PVS<5%, (n=88)	PVS≥5%, (n=296)	p
Mean length of hospital stay (days)	2.8±0.8	4.9±1.2	<0.001
HHF (mean/patient)	1.89±0.2	2.62±0.5	<0.001
WRF (mean change in serum creatinine) (mg/dL)	0.2±0.15	−0.3±0.24	<0.001
CV mortality, n (%)	2 (2.27%)	29 (9.8%)	0.024
All-cause mortality, n (%)	3 (3.41%)	33 (11.15%)	0.035

HHF: Hospitalization for heart failure, WRF: Worsening renal function, CV: Cardiovascular, PVS: Plasma volume shift

and CV mortality (29 in PVS ≥5% vs. 2 in PVS <5%, p=0.0241) were more common in higher PVS group.

DISCUSSION

The effectiveness of the Kaplan–Hakim formula in the quantification of plasma volume expansion ADHF and correlation of the outcome factors with PVS was assessed in this study. Study findings reported a significant plasma volume expansion in ADHF patients. Plasma volume expansion as the major pathophysiology change in ADHF patients is well documented [9]. In a large proportion of ADHF cases, PV expansion operates as a final common pathway leading to congestive symptoms [10]. Although the development of congestion or edema is viewed as a manifestation of PV expansion, it often occurs as the interplay between venous capacitance and plasma volume [11]. Either an increase in plasma volume or decreased venous capacitance increases the filling pressure and congestion develops, leading to leakage of fluid across capillaries. Due to neurohormonal activation, both of these mechanisms are operative in chronic HF [12,13].

Many previous studies have addressed plasma volume estimation in ADHF patients, but most of them had used invasive methods to directly measure the PV, which are cumbersome and cannot be used routinely [14,15]. Since these studies had found a good correlation of PVstatus with in-hospital course, methods to easily measure PV would help in assessing the severity of decompensation, can aid in prognosis and deciding management strategy. The Kaplan-hakim equation by incorporating weight as a measure of net plasma volume and then adding specificity to that parameter by incorporating hematocrit as a reflection of hemodilution reasonably estimates net plasma volume [16]. Our study also reported that the PVS from ideal value significantly affects the duration of stay in the hospital.

Fluid overload in ADHF occurs due to chronic activation of the renin angiosterone and sympathetic system [9,10]. A strong association between guideline-recommended dose of ACEi/ARBs, beta-blockers and normalcy of plasma volume status (p<0.001) was found. Likewise, the use of loop diuretics is associated with a lesser degree of PVS. A similar association was reported with the use of mineralocorticoid antagonists and these findings are similar to the study by Martens *et al*. [17]. This can probably be attributed to treatment bias, as the patients in whom these drugs had been prescribed in fact, had higher plasma volume status and had a greater degree of impairment in cardiac function. Since the number of patients with plasma volume contraction (PVS <0) was less, association between plasma volume contraction and HF medications could not be evaluated. However, previous studies reportedthat patients with LVEF in higher range and those on optimal dosages of ACEi/ARBs had plasma volume contraction. Grodin *et al.* also reported that in the TOPCAT trail, most patients had net plasma volume contraction [18].

The study also reported that the mean duration of stay in the hospital was significantly more in patients with higher PVS. The greater degree of PV expansion requiring longer diuretics use associated renal dysfunction and treatment of other precipitating factors may be the reasons for a prolonged duration of hospitalization. Patients with higher PVS (≥5%) had higher baseline serum creatinine and showed a greater reduction in creatinine after treatment. In contrast, WRF was noted in patients with lower PVS group (or PV contraction) during treatment. In a study by Mullens *et al.* the WRF was associated with venous congestion rather than cardiac index and also reported no relation of WRF with use of diuretics [19]. In our study, we found that though baseline renal dysfunction was greater in patients with higher PVS, the use of diuretics improved renal function rather than worsening it. On the other hand, the use of diuretics in the lower PVS group and with PV contraction was associated with greater WRF, as evident from a greater increase in serum creatinine. This finding has important implications regarding the use of diuretics, as not all ADHF patients have PV expansion and overzealous use of diuretics will result in WRF.

Patients in higher PVS group in our study had significantly repeated number of hospitalizations; all-cause mortality, and cardiovascular mortality during 1-year follow-up. In a study by Martens *et al*, which was conducted in stable HF patients number of HHF & all-cause mortality was higher in patients with higher PVS [17]. Our study also showed the same in ADHF patients with higher PVS.

The correlation of the extent of PVS in current hospitalization persisting for later HHF and mortality even after optimizing HF medications indicates the tendency of these patients towards positive PV status. This is probably due to associated comorbidities, Diabetes and CKD in particular, as underlying renal impairment independently affects PV status. In our study, patients having these comorbidities had higher PVS. Though other complex mechanisms might also be operative contributing to PV expansion, it goes without saying that addressing such comorbidities would, in turn, reduce HHF and mortality. Recently newer anti-diabetic medications, SGLT2 inhibitors in particular through their natriuretic, and diuretic action& by altering myocardial metabolism, have been shown to reduce HHF and mortality [20]. This benefit has been shown even in patients without diabetes; hence, there is scope for further research to explore these complex mechanisms regulating PV status in HF patients and these would be the targets for novel therapeutic strategies in the future.

CONCLUSION

Kaplan–Hakim formula, which incorporates easily available parameters can be routinely used and are more practical and convenient to assess volume status in patients with ADHF. Use of RAAS antagonists and beta-blockers in their optimal dosage is associated with favorable plasma volume status in chronic HF patients and pre-discharge assessment of plasma volume can be used to titrate the dosage of these drugs, including diuretics.

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AUTHORS' CONTRIBUTIONS

Dr. Dipak Ranjan Das and Dr. Biswajit Das - Design and Data collection or processing, editing the manuscript. Dr.Anil Kumar Singh - Analysis and interpretation, literature search, manuscript writing and submission.

CONFLICTS OF INTEREST

Authors declare no conflicts of interest.

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Nil.

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