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Alpha-1-acid glycoprotein and Pro-B-natriuretic peptide evaluation in patients with secondary pulmonary hypertension and end-stage kidney diseases receiving hemodialysis

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ABSTRACT: Pulmonary hypertension (PHT) is a serious condition characterized by increased blood pressure in the pulmonary arteries, leading to reduced blood flow and increased strain on the heart. Secondary PHT refers to cases where is Pulmonary hypertension a consequence of an underlying condition, and one such condition is ESRD. This work aimed to study the role of Alpha-1-acid Glycoprotein (AGP) & Pro-B-Natriuretic Peptide **(**BNP) in the Ddevelopment of PHT in patients under Hemodialysis. A cross-sectional observational study was conducted on 120 patients who visited the Al-Imamain Al-Khadhimain Medical City Hospital, Baghdad, Iraq, between May 2023 and July 2023 and were diagnosed with end-stage renal disease (ESRD) and underwent regular hemodialysis. Levels of AGP and BNP were measured, and clinical characteristics, including gender, age, hemodialysis duration, frequency of hemodialysis sessions per week, body mass index (BMI), and biochemical parameters such as parathyroid hormone (PTH), Ca, PO4, and albumin, were analyzed.Ca levels were significantly higher in the PHT group (8.12 ± 1.09 mg/dL) compared to the NPHT group (7.50 ± 1.10 mg/dL). AGP and BNP levels were significantly elevated in PHT patients (86.50 ± 16.54 ng/ml and 314.79±80.82 pg/ml; respectively) in comparison with NPHT group (41.98 ± 10.89 ng/ml and 211.87 ± 46.24 pg/ml; respectively). the results of the logistic regression analysis indicate that AGP has a significant positive effect on the odds of observing PHT, suggesting that higher AGP levels are associated with an increased likelihood of PHT.Patients with pulmonary hypertension who were receiving hemodialysis also had considerably higher levels of alpha-1-acid glycoprotein and pro-B-natriuretic peptide. These biomarkers might be useful resources for detecting and keeping track of pulmonary hypertension in this patient population.

KEYWORDS: AGP; ESRD; Hemodialysis; Pro-B-Natriuretic Peptide; Pulmonary hypertension.

1. INTRODUCTION

Pulmonary hypertension (PHT) is a serious condition that characterized by gradually rising pulmonary arterial pressure (PAP) and is said to be one of the most common consequences of a number of illnesses, including end-stage renal disease (ESRD) [1, 2]. Among cardiovascular disorders, PHT is the main contributor to right heart failure [1– 6]. PHT is known to represent a unique danger for ESRD patients as well [7]. According to reports, individuals with stage 5 chronic renal disease have an incidence of PHT that ranges from 9 to 39%. ESRD patients who receive hemodialysis have an incidence of PHT that ranges from 8.8 to 68.8% [4]. While PHT can occur in up to 42% of individuals on peritoneal dialysis [8,9]. However, the specific processes underlying PHT in ESRD patients as well as the associated risk factors have not been addressed. According to some researchers, the development of PHT may be influenced by volume overload, severe anaemia, hemodynamic changes, and hyperparathyroidism brought on by renal failure [4, 10- 13]. The fundamental aetiology of PHT in patients with ESRD has also been postulated to be left cardiac

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dysfunction [14]. Additionally, electrolytes and blood components may potentially contribute to PHT. In patients with PHT who have renal failure, several factors are yet unknown [14]. Dialysis or a kidney transplant are required for survival when chronic kidney disease progresses to end-stage kidney disease (ESKD) [15-19]. Long-term hemodialysis will cause the development of PHT, especially when an arteriovenous fistula (Av) is used. There has been an increase in knowledge over the past 15 years that end-stage renal disease (ESRD), in particular, is a risk factor for the emergence of multifactorial pulmonary hypertension. Although the precise mechanism underlying this link is still unknown, it is thought that a number of variables have contributed to it. These include increased cardiac output from arteriovenous fistula (AVF) or chronic anaemia, diastolic dysfunction, chronic inflammation, and chronic volume overload that results in remodelling of the pulmonary vasculature [10].

Alpha-1-acid Glycoprotein (AGP) is an acute-phase protein produced by the liver in response to inflammation and infection (Fournier et al., 2000). Pro- B-Natriuretic Peptide (Pro-BNP) is a precursor to B-type natriuretic peptide (BNP), which is released from the heart in response to increased pressure and volume in the heart chambers [20]. Both of these biomarkers have been studied in various cardiovascular and renal conditions and may have potential relevance in secondary pulmonary hypertension associated with end stage kidney disease and hemodialysis. Hence, we aimed to assess the association between these biomarkers and PHT in patients with CKD.

2. RESULTS

The age and BMI of patients with Pulmonary hypertension (53.17 ± 12.54 years and 27.13 ±7.05 kg/m^2, respectivelly) were non significantly differ ($p>0.05$) from those of non-Pulmonary hypertension group (50.87 ± 14.30 years and 25.76 ±4.44 kg/m^2, respectivelly). Results illustrated in Table 1 showed that the renal function markers, including modification of diet in renal disease (MDRD)/estimated glomerular filtration rate (eGFR) and creatinine levels showed non-significant differences between the Pulmonary hypertension and non-Pulmonary hypertension groups. Urea levels were significantly higher in Pulmonary hypertension patients compared to those without. Calcium levels were also higher in the Pulmonary hypertension group (8.12 ± 1.09 mg/dL) compared to the non-Pulmonary hypertension group (7.50 ± 1.10 mg/dL). On the other hand, highly significant elevations in the levels of Alpha-1-acid Glycoprotein and Pro-B-Natriuretic Peptide were obtained in PHT patients in comparison with NPHT patients. The mean Alpha-1- acid Glycoprotein level was 86.50 ± 16.54 ng/ml in the Pulmonary hypertension group, while in the non-Pulmonary hypertension group, it was 41.98 ± 10.89 ng/ml. The mean Pro-B-Natriuretic Peptide level in the Pulmonary hypertension group was 314.79 ± 80.82 pg/ml, while in the non-Pulmonary hypertension group, it was 211.87 ± 46.24 pg/ml

Results illustrated in Table 2 showed that AGP and BNP were non-significantly correlated with each other, and a positive correlation was observed between calcium and parathyroid hormone levels, which in turn negatively correlated with the levels of AGP. Furthermore, AGP showed to be significantly and negatively correlated with the frequency of hemodialysis, whereas BNP was significantly and positively correlated, in addition to several other less important correlations between studied biochemical markers, as illustrated in Table 2.

Table 3 shows the results of receiver operating characteristic (ROC) curve analysis for alpha-1-acid glycoprotein (AGP) and pro-B-natriuretic peptide (BNP) as differentiating markers between patients with pulmonary hypertension (PHT) and patients without pulmonary hypertension (NPHT). The AUC of the ROC comparison of selected biomarkers is presented in Figure 1, and Table 3 summarizes the ROC criteria findings.

The results suggested that AGP is the best predictor of PHT, followed by BNP, and then MDRD/eGFR. AGP has the highest AUC and the highest sensitivity and specificity. BNP has a lower AUC and lower sensitivity and specificity than AGP, but it is still a good predictor of PHT. MDRD eGFR has the lowest AUC and the lowest sensitivity and specificity of the three biomarkers.

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Table 1. Comparison of Mean Values and Standard Deviations for MDRD/eGFR, Urea, Creatinine, Serum PTH, Ca, PO4, and Albumin between Patients with Pulmonary Hypertension and Patients without Pulmonary Hypertension.

Parameter	Subjects	n	Median	Mean± SD	SEM	P value
MDRD/ Egfr (mL/min/1.73 m²)	PHT	60	6.45	6.20± 1.96	0.25	0.18
	NPHT	60	6.35	6.86± 3.25	0.42	
Urea (mg/dl)	PHT	60	145.55	150.71± 37.12	4.79	0.03
	NPHT	60	132.00	135.60± 39.19	5.06	
Creatinine (mg/dl)	PHT	60	8.95	9.50± 2.59	0.33	0.81
	NPHT	60	8.90	9.36± 3.47	0.45	
S. PTH (pg/ml)	PHT	60	373.50	472.74± 450.65	58.18	0.21
	NPHT	60	326.00	388.53± 257.03	33.46	
Ca (mg/dl)	PHT	60	8.01	8.12± 1.09	0.14	0.002
	NPHT	60	7.60	7.50± 1.10	0.14	
Po4 (mg/dl)	PHT	60	5.20	5.45± 1.62	0.21	0.39
	NPHT	60	4.55	5.16± 1.98	0.26	
Albumin (g/dl)	PHT	60	3.80	3.80± 0.51	0.07	0.54
	NPHT	60	3.70	3.74± 0.60	0.08	
AGP ng/ml	PHT	60	86.67	86.50± 16.54	2.13	< 0.000001
	NPHT	60	41.21	41.98± 10.89	1.41	
BNP pg/ml	PHT	60	301.88	314.79± 80.82	10.43	< 0.000001
	NPHT	60	198.05	211.87± 46.24	5.97	

Table 2. Correlation analysis for various variables measured in the PHT group.

Variables n= 60		AGP	BNP	Albumin	Ca	PO_4	S.PTH[a]	UREA	Cr[b]
BNP	r	0.08							
	p	0.53							
Age	r	-0.09	0.14	0.17	0.02	-0.36	-0.05	0.09	-0.01
	p	0.50	0.30	0.20	0.89	0.00	0.70	0.49	0.93
Albumin	r	0.04	0.00						
	p	0.79	0.98						
BMI	r	0.17	-0.28	0.01	-0.03	-0.02	0.12	-0.07	0.03
	p	0.20	0.03	0.97	0.82	0.88	0.36	0.62	0.83
Ca	r	-0.19	-0.17	0.26					
	p	0.15	0.19	0.04					
PO4	r	0.17	0.11	-0.16	0.23				
	p	0.19	0.42	0.22	0.08				
S.PTH	r	0.59	0.06	0.10	-0.37	0.07			
	p	<0.0001	0.63	0.47	0.00	0.62			
UREA	r	-0.04	0.15	0.07	-0.12	0.33	0.10		
	p	0.79	0.25	0.61	0.37	0.01	0.47		
Cr	r	-0.09	-0.10	0.12	0.36	0.36	-0.13	0.42	
	p	0.48	0.46	0.36	0.00	0.01	0.33	0.00	
Duration	r	0.16	-0.09	0.20	-0.26	-0.14	0.25	-0.04	-0.19
	p	0.21	0.47	0.13	0.05	0.28	0.05	0.77	0.16
Frequency	r	-0.30	-0.17	0.02	0.04	-0.19	-0.01	-0.10	0.12
	p	0.02	0.20	0.88	0.76	0.16	0.94	0.44	0.36
MDRD/ eGFR	r	-0.04	-0.05	-0.11	-0.05	-0.38	-0.15	-0.46	-0.83
	p	0.78	0.68	0.39	0.73	0.00	0.24	0.00	<0.0001

[a] S.PTH: Parathyroid hormone , [b] Cr: Creatinine.

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Table 3. ROC curve analysis for MDRD eGFR, Alpha-1-acid Glycoprotein (AGP) and Pro-B-Natriuretic Peptide (BNP) as they differentiating between Patients with Pulmonary Hypertension (PHT) and Patients without Pulmonary Hypertension (NPHT)

Variable	AUC	SE	95% CI	Cutoff	Sensitivity	Specificity	+LR	-LR
MDRD eGFR mL/min/1.73m²	0.528	0.0533	0.435 to 0.620	≤5	35.00	78.33	1.62	0.83
AGP ng/ml	0.996	0.00325	0.962 to 1.000	>60.046	100.00	96.67	30.00	0.00
BNP pg/ml	0.892	0.0302	0.823 to 0.941	>244.453	85.00	86.67	6.38	0.17

AUC= The area under the curve, (SE)= standard error, 95% CI =95% confidence intervals, +LR =positive likelihood ratios, and LR =negative likelihood ratios

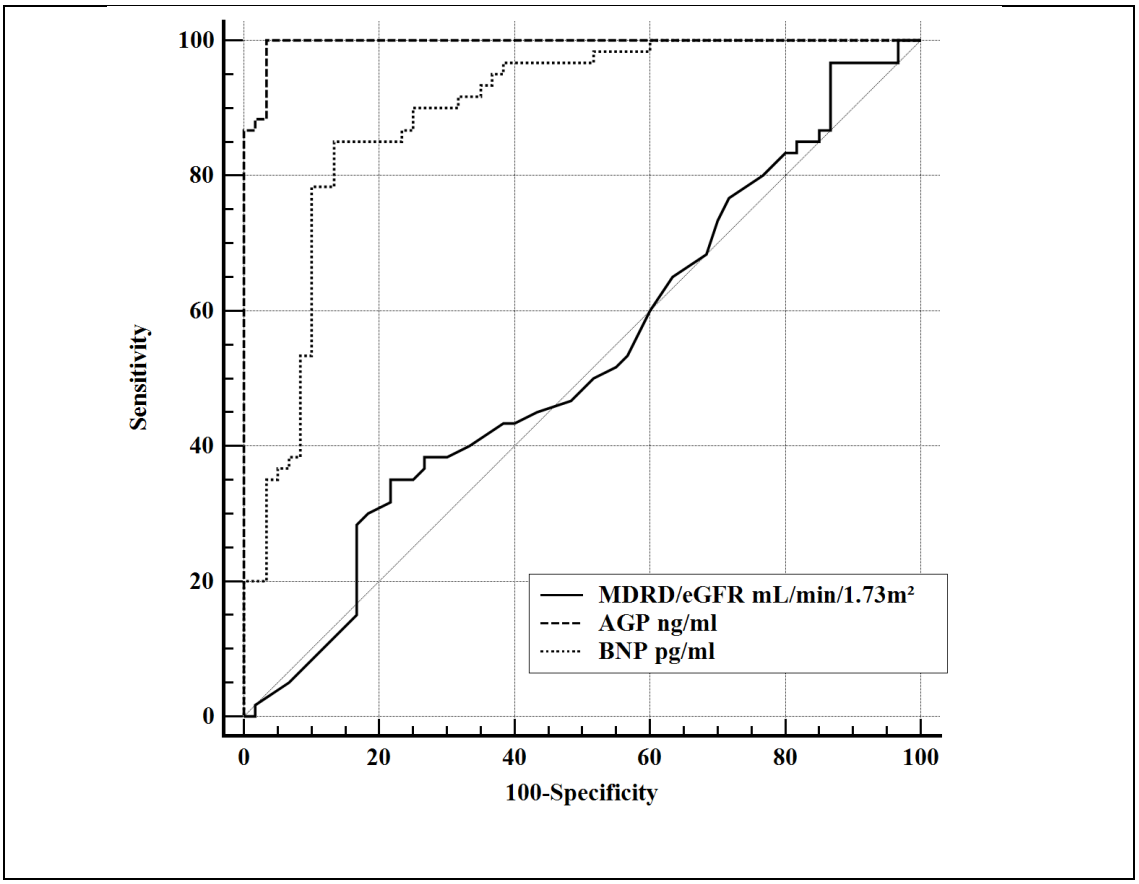

Figure 1. ROC analysis comparison of MDRD eGFR, AGP and BNP showing their respective AUC as they differentiate PHT from NPHT patients

3. DISCUSSION

Among the measures analyzed, only the levels of urea and calcium varied statistically significantly between the two groups. This suggests that patients with pulmonary hypertension and end-stage renal disease had higher urea and calcium levels than those who did not have pulmonary hypertension. Researchers in India examined a variety of factors in a different study, including the level of hemoglobin, blood urea nitrogen (BUN), serum creatinine, and the serum calcium and phosphorus product. According to statistical analysis, only serum creatinine and the Ca product among these variables were substantially linked with pulmonary hypertension [21]. Blood urea nitrogen (BUN), serum creatinine, and hemoglobin levels were observed to substantially correlate with the serum calcium and phosphorus products [22-25]. PHT observed in people with high blood calcium levels may be caused by the increased stiffness of the pulmonary vasculature brought on by vascular calcification.

The study measured AGP levels in two distinct groups—patients with pulmonary hypertension (PHT) and those without pulmonary hypertension (NPHT). AGP is an acute-phase protein produced by the liver in response to inflammation and other physiological stresses. Elevated AGP levels can indicate underlying inflammatory processes. The significant increase in the levels of AGP in PHT patients in comparison with NPHT patients that obtained in the current study suggested that AGP levels are strongly associated with the presence of pulmonary hypertension in patients with end stage kidney disease undergoing hemodialysis. Consistent with our findings, a separate Indian study revealed elevated levels of inflammatory markers, specifically alpha-1-acid glycoprotein and pro- B-type natriuretic peptide, in patients undergoing hemodialysis. Additionally, this study noted reduced ejection fraction, a measure of heart function, which suggested a significant connection with pulmonary hypertension [26]. Likewise, a study conducted in the United States observed higher levels of alpha-1-acid glycoprotein among patients with echocardiogram-based end stage renal disease-associated pulmonary hypertension (ESRD-PH) compared to those without ESRD-PH. This observation aligns with the trend of elevated alpha-1-acid glycoprotein levels being linked to the presence of pulmonary hypertension in kidney disease patients [26, 27]. Furthermore, another study conducted in Brazil reported similar results, adding to the growing body of evidence supporting the association between elevated alpha-1-acid glycoprotein levels and the presence of pulmonary hypertension in patients with kidney disease [28].

The observed disparity in AGP levels between the PHT and NPHT groups implies that AGP could potentially serve as a valuable biomarker for identifying and monitoring pulmonary hypertension in this specific patient population. Monitoring AGP levels over time could provide clinicians with a tool to assess the progression or response to treatment of pulmonary hypertension in individuals with end-stage kidney disease undergoing hemodialysis. Collectively, these studies from different geographical regions bolster the notion that inflammatory markers, specifically alpha-1-acid glycoprotein, might serve as valuable indicators of pulmonary hypertension in individuals with end-stage kidney disease undergoing hemodialysis. The consistent findings across diverse populations underscore the potential clinical significance of these biomarkers in aiding the identification, monitoring, and management of pulmonary hypertension in this high-risk patient group. Moreover, the identification of biomarkers like AGP is crucial for enhancing the early detection and management of pulmonary hypertension, especially in high-risk populations like those with end-stage kidney disease. Early intervention and monitoring can lead to improved patient outcomes and a better understanding of the underlying mechanisms driving the development of pulmonary hypertension in this context.

Another biomarker investigated in the current research was B-type natriuretic peptide (BNP) which also showed to be elevated significantly in PHT patients in comparison with NPHT patients. BNP is a hormone secreted by the heart in response to increased pressure and volume overload. Elevated BNP levels are indicative of heart strain and dysfunction, often observed in conditions like pulmonary hypertension [29]. This emphasizes the strong correlation between elevated BNP levels and the presence of pulmonary hypertension in patients with end-stage kidney disease undergoing hemodialysis. Consistent with our findings, a separate study conducted in the USA involving 88 patients revealed that among individuals with end-stage renal disease (ESRD) being evaluated for renal transplantation, pulmonary hypertension (PH) is notably common [30] (Ariss et al., 2023). Furthermore, the study observed elevated levels of B-type natriuretic peptide (BNP) in these ESRD patients, and these elevated BNP levels were significantly associated with higher pulmonary artery pressure (PAP). These results suggest that BNP has the potential to serve as a valuable non-invasive marker for identifying and assessing pulmonary hypertension in this particular group of patients.

Among the examined biomarkers, only the parathyroid hormone level exhibited a meaningful and statistically significant correlation with the alpha-1- acid glycoprotein (APG) level in patients who had pulmonary hypertension (PHT). This indicates that changes in parathyroid hormone levels are associated with corresponding changes in APG levels in this specific subgroup of patients. The significant correlation between parathyroid hormone and APG levels might have clinical implications. Parathyroid hormone is involved in calcium regulation and bone metabolism, while APG is an acute-phase protein associated with inflammation. The observed correlation could suggest a potential link between calcium metabolism, inflammation, and the development of pulmonary hypertension in these patients. In essence, the study's results point to parathyroid hormone as a biomarker that is notably correlated with the levels of alpha-1-acid glycoprotein in individuals with pulmonary hypertension [31]. This correlation underscores the potential role of parathyroid hormone in the pathophysiology of pulmonary hypertension in this specific patient

population. Further research is needed to elucidate the mechanistic connections and clinical significance of this association. Finally, we test the predication of biomarkers for PHT among patients with ESKD. AGP emerges as the most robust predictor of pulmonary hypertension (PHT), boasting the highest area under the curve (AUC), sensitivity, and specificity. BNP follows AGP in predictive performance. AGP's superior accuracy likely stems from its specificity to pulmonary hypertension, setting it apart from BNP, which can yield elevated values in heart failure patients, leading to potential false positives. AGP's exclusive elevation in pulmonary hypertension renders it a more dependable marker for the disease. These findings hold crucial diagnostic implications, especially for high-risk patients like those with chronic obstructive pulmonary disease or interstitial lung disease. Moreover, AGP could serve not only as a diagnostic tool but also for monitoring PHT progression and treatment response. Nonetheless, given the study's small sample size, these results warrant cautious interpretation.

4. CONCLUSION

Patients with pulmonary hypertension who were receiving hemodialysis also had considerably higher levels of alpha-1-acid glycoprotein and pro-B-natriuretic peptide. These biomarkers might be useful resources for detecting and keeping track of pulmonary hypertension in this patient population.

5. MATERIALS AND METHODS

5.1. Study Design and Settings

A total of 120 patients with End Stage Renal Diseas (ESRD) receiving regular hemodialysis participated in a cross-sectional observational research study. To be eligible, participants had to be at least 18 years old and have been receiving hemodialysis for at least three months. The study was conducted in the Al-Imamain Al-Khadhimain Medical City Hospital's Dialysis Unit in Baghdad, Iraq between May 2023 and July 2023. Using the Eliza Technique, the amounts of pro-B-natriuretic peptide (Pro-BNP) and alpha-1-acid glycoprotein (AGP) in blood samples from all participants were determined. In addition, established methods were employed to measure the concentrations of typical laboratory indicators such urea, creatinine, albumin, and haemoglobin (Hb). PHT was defined as a mean pulmonary arterial pressure (MAP) at rest greater than 25 mmHg. Based on this criterion, the severity of PHT cases was further subdivided into three groups: mild PHT (25–40 mmHg), moderate PHT (40–60 mmHg), and severe PHT (>60 mmHg). The sample population was divided into two groups for analysis:Group 1 was made up of 60 healthy controls who were undergoing hemodialysis but did not have pulmonary hypertension as determined by echocardiography.On the basis of the results of an echocardiography, 60 patients in Group 2 who were receiving hemodialysis had been determined to have pulmonary hypertension.

5.2. Sample collection

Approximately five (5) mls. of venous blood samples are collected. The samples were divided into Two (2) mls. for whole blood hematological assays. The remaining (3) mils. were separated by centrifugation to collect serum then was used to measure both Alpha-1-acid Glycoprotein & Pro-B-Natriuretic Peptide and biochemical assays; Serum (urea, creatinine, and albumin). Samples will be stored at -20 ^{o}C for not more than 1 month or at –70 ^{o}C for 4 months if necessary. (ELISA Routine).

5.3. Statistical analysis

The statistical analysis for this study was performed using Microsoft Excel version 2016 and IBM SPSS Statistics version 21. Analyses involved comparing the means of various parameters between the pulmonary hypertension (PHT) and non-pulmonary hypertension (NPHT) groups. Independent samples t-tests were used for continuous variables such as age, hemodialysis duration, frequency of hemodialysis sessions per week, BMI, and biochemical parameters. The results were reported as means ± SD or medians, as appropriate. Correlation analysis was performed to examine the relationships between variables within the PHT and NPHT groups. Pearson's correlation coefficient (r) was calculated, and p-values were determined to assess the significance of these correlations. Receiver operating characteristic (ROC) curve analysis was conducted to evaluate the diagnostic accuracy of Alpha-1-acid Glycoprotein (AGP) and Pro- B-Natriuretic Peptide (BNP) in differentiating between patients with pulmonary hypertension and those without. The area under the curve (AUC), standard error (SE), 95% confidence intervals (CI), cutoff values, sensitivity,

specificity, positive likelihood ratios (+LR), and negative likelihood ratios (-LR) were calculated. All statistical tests were two-tailed, and a significance level of $p < 0.05$ was considered statistically significant.

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