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Portopulmonary hypertension and serum endothelin-1 levels in patients with liver cirrhosis

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Abstract

A broad body of evidence has accrued, demonstrating the role of endothelin-1 (ET-1) in the pathophysiology of pulmonary arterial hypertension. Furthermore, the role of ET-1 as a causative pathophysiological mechanism of portopulmonary hypertension (POPH) has been consistently implicated; however, there is a lack of satisfactory evidence supporting this assertion. Thus, the present study aims to determine the prevalence of POPH among patients with hepatic cirrhosis, determine the serum ET-1 levels among these patients, and investigate the association between ET-1 and POPH in subjects with hepatic cirrhosis. A prospective, observational study was conducted from September 2017 to August 2018. Detailed history and examination with relevant investigations, including echocardiography, were performed for patients with and without POHP. ET-1 levels were significantly higher among patients with POPH compared to those without POPH. Moreover, the ET-1 cut-off level of 82 pg/mL correctly predicted the 9.3% prevalence of POPH in patients with hepatic cirrhosis with 100% sensitivity and 100% negative predictive value. The ET-1 cut-off level of 82 pg/mL may be used as a biomarker of POPH in patients with hepatic cirrhosis.

Key words: endothelin 1, pulmonary hypertension, portal hypertension, liver cirrhosis, portopulmonary hypertension.

Introduction

Portopulmonary hypertension (POPH) is defined as the coexistence of pulmonary hypertension and portal hypertension in the absence of other clinically evident pulmonary or cardiac diseases [1]. Recent literature studies have estimated that POPH develops in approximately 2-6% of patients with portal hypertension regardless of the presence of concurrent hepatic disease [2]. Interestingly, POPH represents 5-15% of all cases of pulmonary hypertension according to recently published pulmonary arterial hypertension registries [3] . However, the precise prevalence of POPH among patients with concomitant liver cirrhosis still remains not fully understood. In fact, the not very certain prevalence of POPH is attributed to the lack of extensive research on this condition. Furthermore, the limited available studies that have investigated the disorder vary significantly in terms of patient characteristics, diagnostic criteria, and remarkably heterogeneous study designs. On the other hand, the prevalence of POPH is believed to be largely underestimated in many countries, especially where liver cirrhosis is a commonly encountered disorder in clinical practice. Thus, it would be appropriate to at least suspect a diagnosis of POPH especially in patients with liver cirrhosis. However, the presence of nonspecific symptoms of POPH such as dyspnea and fatigue, together with the multiple complex comorbidities associated with patients with liver cirrhosis, make the diagnosis particularly challenging [4].

Despite the difficulties in suspecting POPH, the diagnostic criteria are well-defined. According to the latest guidelines, POPH is diagnosed in patients with portal hypertension or the presence of a portosystemic shunt along with the following hemodynamic criteria; increased mean pulmonary arterial pressure 20 mmHg, pulmonary capillary wedge pressure <15 mm Hg, and pulmonary vascular resistance 240 dyn s cm^{-5} [5]. Right heart catheterization (RHC) is considered the gold standard modality for the diagnosis of POPH due to direct measurement of the mean pulmonary artery pressure. Indeed, right heart catheterization is also deemed essential to stratify and classify the severity of pulmonary hypertension into various categories ranging from mild to severe. Despite right heart catheterization playing a vital role in the diagnosis of POPH, transthoracic echocardiogram (TTE) is often utilized as a screening tool in patients who display progressive dyspnea and hepatic cirrhosis to allow precocious detection of increased systolic pulmonary artery pressure (sPAP).

Notwithstanding the recent advancements of pulmonary hypertension- specific pharmacological therapies and the increased number of performed liver transplantations, the prognostic outcomes in patients with POPH remain to be clearly delineated and data in the literature is severely lacking in this regard. Interestingly, prior to the wide accessibility of pulmonary hypertension targeted therapies, liver transplantation was usually not

performed in most patients with POPH because of the drastic hemodynamic effects of the disorder. Concordantly, liver transplantations were considered an absolute contraindication in the presence of POPH due to the relation of an unacceptable risk of postoperative right heart failure. Despite the lack of research regarding prognostic outcomes in POPH, a recent study conducted by Swanson et al. reported a mean survival rate of 15 months in patients affected by POPH without liver transplant. However, Swanson et al. demonstrated a 5-year survival of 14% in patients taking pulmonary hypertension specific therapies [6]. Despite numerous new trials on the pharmacological treatment for pulmonary arterial hypertension, the evidence for the use of POPH-targeted therapies regarding efficacy and prognostic outcome largely remains scarce. Indeed, the only randomized controlled trial dedicated to the treatment of patient with POPH is with the use of Macitentan. Macitentan is a dual endothelin-receptor antagonist which functions by inhibiting the two endothelin receptor subtypes ET-A and ET-B, preventing ET-1 from interacting with its receptors. Consequently, the randomized controlled trial demonstrated that Macitentan lowered the pulmonary vascular resistance with statistical significance from baseline value [7]. The lack of available data and studies on POPH-targeted specific therapies is likely due to the difficult management of patients with multiple comorbidities and the complexity of the pathogenesis of the disease itself.

The precise pathophysiological mechanisms of POPH remain to be delineated, however, recent studies have suggested a delicate interplay between systemic haemodynamic factors and hepatic/pulmonary local vasoconstrictor factors. Contemporary research has implicated some of the following causative and contributory mechanisms including but not limited to: excessive local production of vasoconstrictor substances in the lung [8-10] such as endothelin-1 (ET-1), increased pulmonary blood flow which contributes to endothelial damage and vascular remodelling by induction of a pro-inflammatory response [11], excessive pulmonary vascular volume [12], and in situ micro-thrombosis [13,14]. Despite the lack of data regarding the underlying precise pathophysiological mechanisms, ET-1 has almost always been regarded as an important contributor to the pathogenesis of POPH [15-17]. Much interest has stemmed in the importance of ET-1 in contributing to and propagating POPH due to its potent vasoconstrictory action. Indeed, ET-1 is the most potent vasoconstrictor of the three isoforms of endothelins and is therefore assumed to be responsible for most of the biologic effects exerted by the endothelin subclass [15]. Nonetheless, the precise role of ET-1 in POPH remains to be elucidated and further studies are evidently required.

As such, considering that the prevalence of POPH is largely unknown, our earlier investigations focused on assessing the prevalence of POPH in patients with hepatic

cirrhosis. Furthermore, we evaluated the association of clinical features and echocardiographic variables in relation to POPH [18]. Moreover, the role of ET-1 in POPH has been consistently implicated in the literature. Hence, the aim of the current study was to determine serum ET-1 levels in patients with hepatic cirrhosis and to further investigate the association of ET-1 with the presence of POPH.

Materials and Methods

A prospective, observational study was conducted at King George's Medical University from September 2017 and August 2018 in collaboration with the University of Rome Tor Vergata. The study included inpatient department patients aged 18–65 years with chronic liver disorders such as jaundice, edema, ascites, hypersplenism, lower esophageal varices, deranged liver function tests and Child Pugh scores, surface nodularity and coarse and heterogenous liver texture determined on ultrasonography. Patients with congenital heart disease, valvular heart disease, pulmonary veno-occlusive disease, left ventricular disease, pulmonary capillary hemangiomatosis, lung disease, lung and liver transplantation, liver tumours, spleen resection, connective tissue disorders, thyroid gland disorders, sickle-cell disease and related conditions, sarcoidosis, human immunodeficiency virus infection, bacterial infection, current smokers, clinical history of peripheral venous thrombosis or Budd-Chiari syndrome, and adherence to fenfluramine or its derivatives, amphetamines, dasatinib, or interferon-alpha were excluded from the study. This study was approved by the Institutional Ethics Committee (protocol code ECR/262/Inst/UP/2013/RR-16). All patients provided written informed consent for study participation. The study was conducted in accordance with the Declaration of Helsinki.

Diagnosis

Pulmonary hypertension was diagnosed as mean pulmonary arterial pressure 25 mmHg in line with the 2015 European Society of Cardiology and European Respiratory Society (ESC/ERS) Guidelines for the diagnosis and treatment of pulmonary hypertension. Pulmonary hypertension was also diagnosed through echocardiographic means in line with the 2015 ESC/ERS Guidelines on pulmonary hypertension. Pulmonary capillary wedge pressure was not measured, thus, and mitral E/A ratio was measured and those falling in grade III left ventricular diastolic dysfunction were excluded. Portal hypertension was diagnosed according to ultrasound-based criteria: (i) dilated portal vein (>13 mm); (ii) biphasic or reverse flow in portal vein; (iii) portal-systemic collateral pathways (collateral vessels/varices), (iv) splenomegaly; or (v) ascites. Mild/moderate ascites was defined as diuretic responsive whereas severe ascites was defined as diuretic refractory[18].

Echocardiography was performed in accordance with the recommendations of the European Association of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE) [19,20]. The echocardiography machine used was VIVID E95 (GE Healthcare, Chicago, IL, USA).

Endothelin-1 assay

The human ET-1 Kit used a double antibody sandwich enzyme linked immunosorbent one-step process assay (ELISA) to assess the level of ET-1 in samples. Standard, test sample and horseradish peroxidase (HRP) labelled ET-1 were added to enzyme wells which were precoated with ET-1 antibody. Next, incubation was allowed followed by washing to remove the uncombined enzyme. Upon adding chromogen solution A and B, the colour of the liquid changed into blue, and the reaction with the acid caused the colour to become yellow.

Data collection

Data for patient demographics and laboratory findings were collected and compared among patients with and without POPH.

Statistical analysis

Categorical variables are expressed as frequency and percentages and continuous variables are expressed as mean ± standard deviation. Categorical variables were compared using chi-square test. Continuous variables were compared using unpaired t-test. A p value <0.05 was considered statistically significant. The statistical evaluation of data was done using the using Statistical Package for Social Sciences version 20 (IBM Corp., Armonk, NY, USA).

Results

Baseline demographics

A total of 86 patients with hepatic cirrhosis were enrolled in the study, comprising 8 patients with Portopulmonary Hypertension (POPH) and 78 patients in the non-POPH group. POPH was diagnosed in 8 (9.3%) patients with hepatic cirrhosis. There were no significant difference in age (p=0.85) and sex (p=0.27) in both the groups .High-sensitive cardiac troponin levels were 0.02 ± 0.004 ng/ml and 0.03 ± 0.03 ng/ml in patients with and without POPH, respectively. ET-1 levels were (81.68 ± 14.98 pg/ml vs 37.38 ± 15.12 pg/ml ,p=.0001) higher in patients with POPH. This was a statistically significant finding. The baseline demographics are outlined in Table 1.

Predictive values of endothelin 1 level in identifying pulmonary hypertension patients

ET-1 cut-off level of 82 pg/ml correctly predicted POPH in 9.3% patients with hepatic cirrhosis with 100% sensitivity [95% CI: (100.0–100.0)], 85.9% specificity [(95% CI: (78.2-93.6)], 42.1% positive predictive value [(95% CI: (19.9–64.3) and 100% negative predictive value [(95% CI: (100.0–100.0)]. Area under the curve was 0.98 (0.94–0.99). The values of ET-1 level used in identifying pulmonary hypertension patients are shown in Table 2 and Figure 1.

Discussion

POPH is an uncommon complication of hepatic cirrhosis, and its precise prevalence remains to be elucidated due to differences in study designs, patient features and diagnostic criteria utilized between different research groups. Due to the presence of a specific symptoms, and the existence of multiple comorbidities amongst patients affected by POPH, there is an essential requirement in having a multidisciplinary approach to managing this condition and a strong suspicion index between clinicians is quintessential.

ET-1 is a potent vasoconstrictor and there are many studies implicating its role in both the cause and propagation in pulmonary hypertension by inducing vasoconstriction and inducing vascular remodelling. Despite the well-elucidated role of ET-1 in pulmonary hypertension as demonstrated by multiple recent studies, its association with hepatic cirrhosis and POPH remains largely unclear. The lack of satisfactory data regarding the prevalence of POPH and the unclear role of ET-1 in the disorder is the reason we performed this study. Indeed, the aims of our current study were two-fold: (i) to determine the prevalence of POPH in patients with hepatic cirrhosis and (ii) to investigate the association of ET-1 with POPH.

Recently conducted research has estimated that the prevalence of POPH ranges from 1.0%–16.0% [2,21-25]. The high variation range amongst studies are due to differences in patient characteristics, type of study carried out and the diagnostic criteria used in the diagnosis of POPH. POPH onset frequently occurs in end-stage liver disease, and typically affects patients and candidates undergoing or requiring hepatic transplantation. Accordingly, considering the myriad of a specific symptoms in patients with hepatic cirrhosis and the complexity in managing these patients there is most likely a significant underestimation in the prevalence of POPH. Indeed, the presence of a specific symptoms confirms the need to have a clear idea on the prevalence of POPH and to understand the role of ET-1 in the pathogenesis. Consequently, raised circulating ET-1 concentrations have been reported in patients with liver cirrhosis, particularly in those with advanced liver disease [26], and this increases proportionally with the severity of functional liver impairment. Indeed, patients

with advanced cirrhosis and ascites presented with ~fivefold elevated plasma ET-1 concentrations compared with twofold increased levels in patients with compensated cirrhosis [27] implicating its quintessential role in the pathogenesis and aetiology in contributing to POPH. The current study reveals 9.3% prevalence and this finding is in line with several other studies conducted among varying cohorts as shown in Table 3.

The precise underlying pathophysiological mechanism of portal hypertension are unclear however, it is thought to be caused by a combination of hyperdynamic circulation attributed to peripheral arterial vasodilation and consequent reduced peripheral vascular resistance as a trigger for secondary neurohumoral activation and due to localized release of ET-1 which exerts its vasoconstrictor properties locally [28]. In line with this, there are several studies that seem to suggest that elevated systemic ET-1 concentrations originate locally from hepato-splanchnic release. Accordingly, Pinzani et al. demonstrated that there is an increase of ET-1 mRNA and consequent protein expression in human cirrhotic liver, [29]. Other studies have identified that the sinusoidal endothelial and stellate cells are the major synthesis sites of ET-1 in hepatic cirrhosis [30] which further implicate the role of ET-1 with POPH.

Thus, the current study aimed to investigate the association between ET-1 levels and POPH in patients with hepatic cirrhosis. To the best of our knowledge, this is the first such study in our country. Study findings revealed an ET-1 cut-off level of 82 pg/ml correctly predicted 9.3% prevalence of POPH in patients with hepatic cirrhosis with 100% sensitivity and 100% negative predictive value suggestive of an association between ET-1 levels and POPH. Moreover, these findings support observations from an earlier study [15] that revealed higher ET-1 levels in patients with POPH than in patients without POPH [9.1 (1.6-20.7) vs. 2.5 (1.4-9.2) pg/mL, p=0.02]. Moreover, ET-1: ET-3 ratio was higher in patients with POPH. Similarly, a second study [1] also documented 4.5 ± 2.8 pg/mL, 2.0 ± 1.2 pg/mL, and 1.8 ± 0.8 pg/mL in patients with POPH, hyperdynamic circulation, and cirrhosis, respectively. ET-1 levels were almost two-fold greater in patients with POPH. A third study [31] similarly revealed ET-1 levels in all study patients as a whole were significantly higher than levels in normal controls. There was a statistically significant difference in ET-1 levels between patients with and patients without POPH (p=0.02).

Study limitations

There are a few study limitations that deserve honourable mention including the relatively modest sample size used in our study. Furthermore, after the conduction of this research, novel guidelines redefining POPH have been published, and the impact of these guidelines in routine clinical practice needs to be further explored. In addition, thoracic computed

tomography (CT) was not performed, and as such we could not rule out the presence of interstitial lung disease which may independently contribute and propagate pulmonary hypertension. Also, the diagnostic criteria used in this study were performed by echocardiography rather than the gold standard invasive right heart catheterization. In spite of this, recent studies have demonstrated that echocardiography displays high sensitivity, specificity, positive predictive value, negative predictive value, and exhibits high accuracy for the diagnosis of POPH [32].

Conclusions

Our study showed that ET-1 levels were significantly higher among patients with POPH compared to those without POPH.

ET-1 cut-off level of 82 pg/ml levels may find use as a biomarker of POPH in patients with hepatic cirrhosis, however further studies are required to confirm this observation.

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Table 1. Baseline demographics characteristics.

Variable	POPH present(n=8)	POPH absent(n=78)	p
Age, years			
<40	3 (37.5%)	30 (38.46%)	
40–50	1 (12.5%)	15 (19.23%)	0.85
51–60	3 (37.5%)	19 (24.35%)	
>60	1 (12.5%)	14 (17.94%)	
Males(n=67)	5 (62.5%)	62 (92.5%)	0.27
High-sensitive cardiac troponin T, ng/ml	0.02 ± 0.004	0.03 ± 0.03	0.87
Endothelin-1, pg/ml	81.68 ± 14.98	37.38 ± 15.12	**0.0001***

All data are expressed as number (percentage) or mean ± standard deviation; p-value <0.05 was considered statistically significant.

Table 2. Predictive values of endothelin-1 level in identifying pulmonary hypertension patients.

Endothelin-1 (pg/ml) level	POPH present n(%)	POPH absent n(%)
>82	8 (9.3%)	0 (0%)
82	0 (0%)	78 (90.7%)
Total	8 (9.3%)	78 (90.7%)

Predictive value, % (95% CI)	
Sensitivity	100.0 (100.0-100.0)
Specificity	85.9 (78.2-93.6)
Positive predictive value	42.1 (19.9-64.3)
Negative predictive value	100.0 (100.0-100.0)
Area under the curve	0.98 (0.94-0.99)

Table 3. Prevalence of POPH among variable patient cohorts.

Sr. No.	Authors	Study design	Patient number	Patient subset	Prevalence	Definition of POPH	Diagnostic modality
1	Atsukawa et al.[28]	Retrospective	186	Portal hypertension and hepatic cirrhosis	1.1%	Mean pulmonary artery pressure 25 mmHg, pulmonary vascular resistance 3 WU and pulmonary artery wedge pressure 15 mmHg	Right heart catheterization
2	Chiva et al. [29]	Retrospective	600	Portal hypertension and hepatic cirrhosis	1.7%	Mean pulmonary artery pressure 25 mmHg, pulmonary vascular resistance >240 dyn s cm^{-5} and pulmonary capillary wedge pressure; <15 mmHg (or pulmonary capillary wedge pressure; 15 mmHg with transpulmonary gradient; 12 mmHg)	Right heart catheterization
3	Shao et al.[30]	Retrospective	188	Portal hypertension	2.8%	Mean pulmonary artery pressure 25 mmHg, pulmonary vascular resistance 3 WU and pulmonary artery wedge pressure 15 mmHg	Echocardiography
4	Navarro-Vergara et al. [31]	Retrospective, transversal descriptive and analytical study	244	Pulmonary arterial hypertension	6.1%	Portal hypertension (inferred from presence of splenomegaly, thrombocytopenia portosystemic shunts, esophageal varices or portal vein abnormalities, or confirmed by hemodynamic measurements such hepatic venous pressure gradient (HVPG) > 5 mmHg; and pulmonary arterial hypertension mean pulmonary arterial pressure >20 mmHg at rest, pulmonary capillary wedge pressure <15 mmHg, and pulmonary vascular resistance 3 WU	Right cardiac catheterization
6	Gupta et al.[18]	Prospective, observational	86	Hepatic cirrhosis	9.3%	Pulmonary artery pressure 25 mmHg, pulmonary vascular resistance 3 WU and pulmonary artery wedge pressure 15 mmHg	Echocardiography
7	Chen et al. [32]	Prospective	100	Hepatic cirrhosis and hospitalized	10%	Pulmonary artery systolic pressure 40 mmHg	Echocardiography

8	Tsiakalos et al. [15]	Prospective	57	Hepatic cirrhosis	15.8%	Pulmonary arterial pressure 40 mmHg and pulmonary acceleration time <100 ms	Echocardiography
9	Benjaminov et al. [26]	Retrospective	62	Hepatic cirrhosis and refractory ascites	16.1%	Presence of portosystemic shunting, mean pulmonary artery pressure greater than 25 mm Hg, (3) pulmonary vascular resistance >120 dyn s cm^{-5} and pulmonary artery wedge pressure <15 mmHg	Right cardiac catheterization and echocardiography

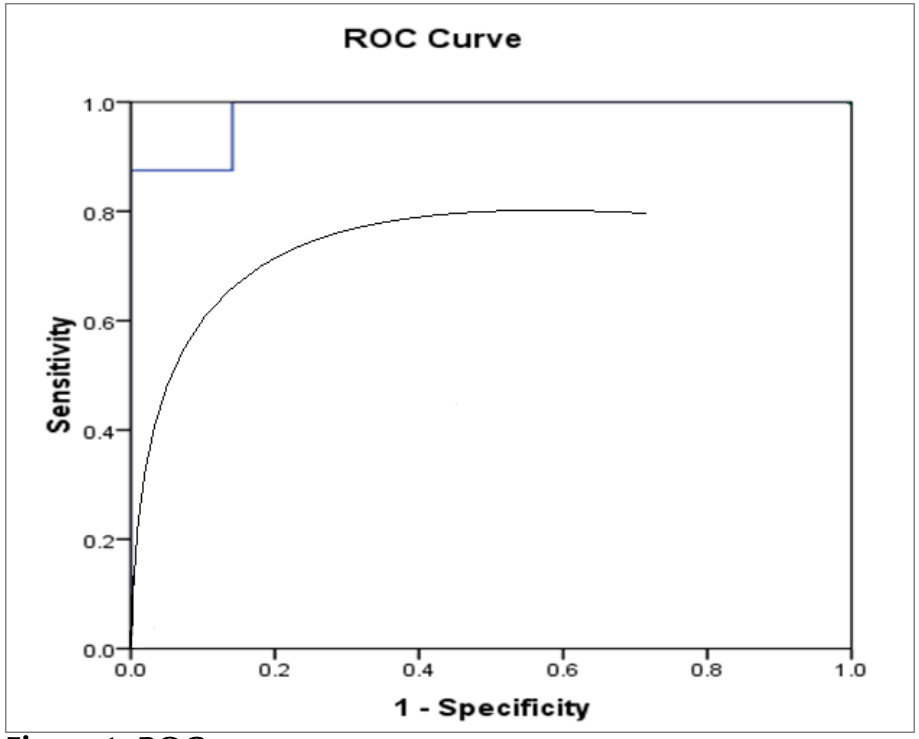

Figure 1. ROC curve.