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EVALUATION OF SAFETY AND EFFICACY OF ARGON PLASMA COAGULATION IN TREATMENT OF PORTAL HYPERTENSIVE GASTROPATHY IN EGYPTIAN PATIENTS WITH LIVER CIRRHOSIS

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ABSTRACT

Background: Portal hypertensive gastropathy (PHG) occurs as a complication of cirrhosis or non-cirrhotic portal hypertension. Endoscopic ablation of PHG is gaining popularity nowadays. Argon plasma coagulation (APC) is a non contact thermal method of hemeostasis. **Aim of the work:** The study **a**imed to evaluate the efficacy and safety of APC as a tool of management of patients with severe portal hypertensive gastropathy due to liver cirrhosis. **Methods: A** prospective study was conducted from the period between January 2017 to July 2017 on 30 persons who fulfilling the designed inclusion criteria. Cirrhotic patients were prospectively included in this study if they presented with overt or occult bleeding related to portal hypertension. Success was defined as; control of bleeding, or significant Hb increase from pretreatment level, All patients were subjected to full history taking, through clinical examination, routine laboratory investigations, Occult blood in stool, abdominal ultrasound, and upper GIT endoscopy. **Results:** All patients had severe portal hypertensive gastropathy, 19 patients (63.3 %) had their lesions in the body and fundus, 5 patients (16.7 %) had their lesions in the body, fundus and antrum, 4 patients (13.3 %) had their lesions in the body and 2 patients (6.7 %) had their lesions in the fundus only. APC was done for 30 patients with severe PHG and followed in serial sessions (3 - 4 weeks interval) up to 3 sessions and duration of follow up was 6 months, 22 patients (73.3 %) of severe PHG changed into mild form of PHG. **Conclusion:** APC is effective and safe in the treatment of cirrhosis-related sever portal hypertensive gastropathy and our study suggests that APC should be considered as the treatment of choice in sever portal hypertensive gastropathy.

KEYWORDS: *Argon plasma coagulation, cirrhotic patients, Portal hypertensive gastropathy.*

INTRODUCTION

Portal hypertensive gastropathy (PHG) occurs as a complication of cirrhosis or non-cirrhotic portal hypertension. PHG is clinically important because it may cause acute (and even) massive, or insidious, blood loss ***(Gjeorgjievski et al., 2016).*** Advances in argon plasma coagulation may result in novel treatment options for portal hypertensive gastropathy ***(Tjwa et al., 2014)***

AIM OF THE WORK

The aim of this work is to evaluate the efficacy and safety of argon plasma coagulation by labratory parameters and endoscopically in the management of patient with severe portal hypertensive gastropathy due to liver cirrhosis.

PATIENTS AND METHODS

A prospective study was carried out to find the efficacy and safety of argon plasma coagulation by labratory parameters and endoscopically in the management of patient with severe portal hypertensive gastropathy due to liver cirrhosis. The study was carried out from Outpatient Clinic and inpatients of Tropical medicine department Al-Azhar University Cairo, Egypt. The study was conducted over a 6-month period from January 2017 to July 2017 on 30 persons who fulfilling the designed inclusion criteria (Age ≥18 years, Egyptian patients, and patients with liver cirrhosis that had severe portal hypertensive gastropathy that causes chronic blood loss. Patients with peptic ulcer disease, or previous surgical treatment of PHT,or history of prolonged use of non-steroidal anti-inflammatory drugs, or patients with renal, cardic, cancer, and collagenic disorders were excluded from the study. All patients involved in the current study were informed about the nature and details of the current work and a written consent was obtained for each participant. The study was approved by the local Ethics Committee, Faculty of Medicine, Al-Azhar University. All the patients of current study were subjected to full history taking, through clinical examination with special emphasis on abdominal examination and signs of liver disease(hepatomegaly, splenomegaly and ascites), routine laboratory investigations, occult blood in stool, abdominal ultrasound to detect the presence of liver cirrhosis, presence of portal hypertension(portal vein diameter and presence of collaterals), presence of ascites

and its degree and splenomegaly, and finally upper GIT endoscopy. Data were analyzed using the SPSS/Win (version 13) software. The arithmetic mean ($\overline{X}$) and the standard deviation (SD) were used as measures of central tendency and dispersion of data, respectively. The student "t" test was used to compare between two mean values. Difference between groups were tested for statistical significance using the Chi-square (X^2) test and spearman coefficient and Anova test. Results were considered significant when P value is 0.05 or less.

RESULTS

This study was carried out on 30 patients with liver cirrhosis, portal hypertension and suffering from severe portal hypertensive gastropathy that constitute a source of chronic blood loss. They were subjected to clinical, laboratory, and endoscopic evaluation before applying APC and 6 months after. Demographic data of the studied group reveals age of patients ranged between 46 and 61 with a mean of 52.43 years. The male gender was predominant, representing 63.3 % of the whole group and the female gender representing 36.7 % of the studied group**.** 23 patients (76.7 %) reported living in rural areas, while 7 patients (23.3 %) were living in urban area.

Clinical data of the studied group reveals previous GIT bleeding in 20 patients (66.7 %) gave, 7 of them (35 %) reported its type as hematemesis and melena, while 13 patients (65 %) reported that they had melena **(figure 1).** Previous EVL/EVS was done in 21 patients (70 %) reported (3patients had EVS and 18 patients had EVL). Clinical signs of the studied group shows Jaundice was found in 24 patients (80 %), pallor was found in 21 patients (70 %), lower limb edema was resent in 17 patients (56.7 %), hepatomegaly was found in 1 patient (3.3 %), splenomegaly was found in 30 patients (100 %), ascites was found in 28 patients (93.3 %)**.** Liver cirrhosis was evident in 29 patients (96.7 %) by abdominal ultrasonography.

AST ranged between (12–90 U/L) with a mean of 44.77±20.66. Serum albumin ranged between (2 - 2.9 mg/dl) with a mean of 2.63±1.05, ALT ranged between (12–130 U/L) with a mean of 52.8±28.67. Serum bilirubin ranged between (1 – 5 mg/dl) with a mean of 2.62±1.05**.** Prothrombin time ranged between (16.2 – 21.4 sec) with a mean of 18.35±1.5. **Table (1).**

Table 1: Laboratory liver profile of studied patients (n= 30).

	SGPT (U/L)	SGOT (U/L)	Serum Bilirubin (mg/dl)	Serum Albumin (mg/dl)	Prothrombin Time (sec.)	INR
Min	12	12	1	2	16.2	1.4
Max	130	90	5	2.9	21.4	2.3
Mean	52.8	44.77	2.62	2.63	18.35	1.72
±SD	28.67	20.66	1.05	0.27	1.5	0.21
Occult blood in stool:						
Positive	25 (83.3 %)					
Negative	5 (16.7 %)					

Stool analysis was positive for occult blood in 25 patients (83.3 %). Hepatitis viral markers: 29 patients (96.7 %) had hepatitis C antibodies and 1 patient (3.3 %) had hepatitis B surface antigen**.**The hemoglobin of the studied group ranged between (7.6: 10.8 g/dl) with a mean value of 9.12±0.82 before applying the APC and after applying APC it ranged between (7.9: 11.2 g/dl) with a mean value of 9.91±89. The difference between the hemoglobin level before and after APC was statistically significant (p= 0.000).

The hematocrit level of the studied group ranged between (22.8: 32.2) with a mean value of 27.53±2.84 before applying the APC and after applying APC it ranged between (22: 33) with a mean value of 29.41±2.84. The difference between the hematocrit level before and after APC was statistically significant (p= 0.000).

Child-Pugh-Turcotte score of the studied patients ranged between (7: 12) with a mean value of 9.7±1.72. According to this score, 15 patients (50 %) were child class B and 15 patients (50 %) were child class C. **Table.(2).**

Table 2: Child score of studied patients (n=30).

	Studied patients
Child score:	
Min	7
Max	12
Mean	9.7
±SD	1.72
Child class:	
A	0 (0 %)
B	15 (50 %)
C	15 (50 %)

The Endoscopic features shows that 29 patients (96.7 %) of the studied group have OV. Band ligation were done in 21 patients who had OV F2 with risk signs and OV F3 till complete eradication. Injection sclera-therapy not did to any patiens**.** Gastric varices were found in 3 patients (10 %) with no risk signs.

All patients had severe portal hypertensive gastropathy (100 %). 19 patients (63.3 %) had their lesions in the body and fundus, 5 patients (16.7 %) had their lesions in the body, fundus and antrum, 4 patients (13.3 %) had

their lesions in the body and 2 patients (6.7 %) had their lesions in the fundus only. **Table (3).**

Table 3: Endoscopic features before APC of studied patients (n=30).

	Studied patients
Esophageal varices:	
Absent	1 (3.3 %)
Present	29 (96.7 %)
Ov banded:	
Absent	9 (30 %)
Present	21 (70 %)
Injection sclera-therapy:	
Absent	30 (100 %)
Present	0 (0 %)
Gastric varices:	
Absent	27 (90 %)
Present	3 (10 %)
PHG degree:	
Mild	0 (0 %)
Severe	30 (100 %)
Distribution of PHG:	
Body	4 (13.3 %)
Fundus	2 (6.7 %)
Body & fundus	19 (63.3 %)
Body, fundus &antrum	5 (16.7 %)

There is an evident association between the high score of the Child-Pugh score and the presence of OV. The number of APC sessions applied were ranged between (2: 3) with a mean of 2.43±0.5.

Table 4: Comparison between endoscopic picture of PHG before and after APC.

PHG degree	Before APC	After APC	X^2	p-value
Mild	0 (0 %)	22 (73.3 %)	41.23	0.000*
severe	30 (100%)	8 (26.7 %)		

*: Statistically significant at $p \leq 0.05$

Table (4) shows highly statistical significant difference **(p-value = 0.000)** between PHG degree before and after APC **(figure 26).**

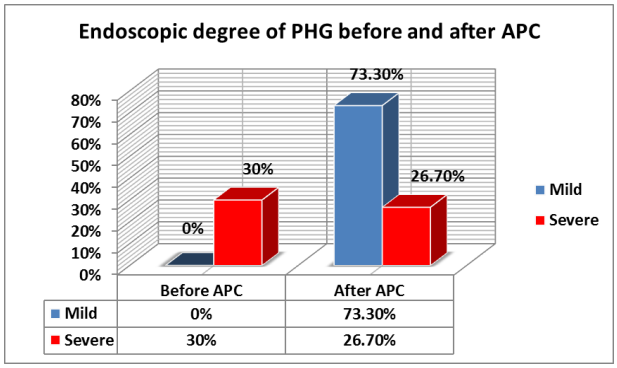

Figure 1: Endoscopic degree of PHG before and after APC.

DISCUSION

This study was performed to evaluate the safety and efficacy of argon plasma coagulation in treatment of portal hypertensive gastropathy in patients with liver cirrhosis.

In our study, the age of our patients ranged between 46 and 61 years. This goes with ***Strasser et al. (1995), Ghany et al.(2016),*** who found on a univariate analysis, that the presence of cirrhosis correlated with older age, and on multivariate analysis, the only significant predictor of cirrhosis was age. They added that patients with clinical evidence of portal hypertension were on the average of 15 years older than those with histological cirrhosis only.

Seventy three percent of our patients were from rural areas, and 27 % were from urban areas, this results were in agreement with ***Mohamed et al.(1995), El Feki et al.(2013),*** who reported that most of HCV infection in Egypt are common in rural areas rather the urban ones.

In our study, twenty patients (70 %) had history of previous GIT bleeding whether melena or hematemsis. Also all of our patients had severe PHG and 21 patients had EV grade F2 and F3, these result goes with that of ***Cioni et al.(1996),*** who demonstrated a correlation between both OV and PHG and the increased incidence of GIT bleeding.

In our study, we have positive history of variceal intervention in 21cases. There is a controversy regarding whether or not PHG that occurs in the context of endoscopic therapy is a clinically relevant. ***Yüksel et al.(2006),*** suggested that variceal obliteration aggravates PHG. This aggravation is probably caused by enhancement of gastric mucosa congestion by acute blockade of mucosal blood flow, Also, **EL-Kayat et al.(2010), Poddar et al.(2011),** demonstrated that endoscopic therapy has been associated with increased incidence of PHG.

On the other hand, several studies support the opposite, ***Huo et al.(1995),*** demonstrated that PHG that occurs after endoscopic sclerotherapy or ligation is transient. Also, ***Primignani et al.(2000),*** reported in his study in which 315 patients with liver cirrhosis were followed up clinically and endoscopically every 6 months for 3 years, and particularly for the natural history and evolution of PHG over time. It showed that 25 % of patients showed fluctuating appearance on sequential endoscopies, with transition from none to mild to severe and vice versa, in about 29 % of patients, however, the endoscopic picture was stable through the follow up period, while it showed steady deterioration in about 23 % and a sustained improvement in another 23 %. From this observation, the authors came to conclusion that PHG is a rather dynamic condition which can progress overtime from mild to severe and vice versa.

In our study, gastric varices were found in 3 patients and that goes with ***Iwao et al.(1997), Wu et al.(2015),*** that demonstrated that PHG develops less frequently in patients having a well-developed fundal varices than in those with no or poorly developed fundal varices. Since fundal varices are usually formed by a gastrorenal shunt, this finding supports the view that the presence of gastrorenal shunt may play a protective role in the development of PHG after variceal ligation.

In our study, each of pallor and anemia were detected significantly in our patients,this reflects the risk of chronic bleeding from severe PHG. This is in agreement of ***Gjeorgjievski et al.(2016),*** who documented significant risk of minor or chronic bleeding in severe PHG.

All our patients had anemia, and according to ***Minemura et al.(2009),*** it may not only be attributed to chronic blood loss, nutritional deficiencies or red cell hemolysis by hypersplenism, but also to the presence of humoral inhibitors of hematopoetic proginator cells in the serum of cirrhotic patients.

Also, the mean value of platelets was low. Thrombocytopenia is a common feature of cirrhosis, and many mechanisms were incriminated for its pathogenesis. Hypersplenism, platelet associated immunoglobulins, as well as significant decline of serum thrombopoitien level as reported by ***Tana et al.(2015).***

In our study, we found that hyperbilirubenimia, hypoalbuminemia and low Prothrombin activity were common laboratory findings in our patients, giving the assumption that the severe from of PHG are associated with more severe liver affection, These go with ***Zardi et al.(2015),*** who report that presence of such findings could be related to the disturbed liver function in patient with advanced cirrhosis.

All our patients had Child-Pugh score (B and C) and this goes with ***Merli et al.(2004), Fontana et al.(2006),*** who report that PHG is frequently observed in patients with more severe liver disease.

Other as ***Merkel et al.(2003),*** had controversy results as they reported that there is no relationship was found between hepatic function, as assessed by Child-Pugh score and PHG.

All our patients had splenomegaly, the longitudinal diameter of the spleen ranged between 14- 20 cm with a mean value of 16.17 ± 2.31 cm. ***Colecchia et al.(2012),*** reported that splenic size was increased in portal hypertension patients and this is in agreement with our study, where all our patients had splenomegaly. Also, all our patients had increased portal vein diameter with a mean of 14.8± 2 mm which is considered one of the sonographic features of portal hypertension.

A positive correlation has been found between portal pressure and portal vein diameter, ***Heller et al.(2014)*** reported that a dilated portal vein diameter suggests portal hypertension.

In our initial upper GIT endoscopy, 29 patients had OV,21 patients of them had OV F2 and F3 who where on eradication sessions. This goes with ***Urrunaga et al.(2014)*** who succeeded to prove that both frequency and severity of PHG in cirrhotic patients were significantly correlated to the presence and grade of OV. Band ligations till eradication were done in 21 patients who had F2 with risk signs and F3.

Evident association was found between the presence of OV and the advanced liver state represented by high Child- Pugh score.

All our patients had severe PHG. The lesions predominately were found in the body and the fundus rather than on the antrum, with a percentage of 63.3%. This was found to be in agreement with ***Semenova et al.(2014),*** who stated that PHG lesions are often typically found in the fundus and body(proximal to the antrum). Also, ***Qureshi et al.(2014),*** stated that PHG was more frequently observed in the fundal and corporeal mucosa rather than the antrum. Being more perfused, the fundal and corporeal mucosal were in their opinion more susceptible to circulatory congestion in cirrhotic patients with portal hypertension.

The APC sessions ranged between 2 and 3 times with a mean of 2.43± 0.50. This goes with ***Herrera et al.(2008),*** who reported that we can use APC in treatment of bleeding gastric lesions effectively with few treatment sessions.

On comparing laboratory investigations of our patients between the first visit and the follow up 6 months period, there was a significant increase in the hemoglobin and hematocrit level and there was overall improvement of anemia. This could be attributed to the establishment of successful hemostsis by APC, which helped in eliminating the expected source of chronic blood loss.

This results were close to ***Gonzalez-Suarez et al. (2003),*** that studied the effect of APC on bleeding from PHG where 22 cirrhotic patients (16 patients had chronic anemia and 6 patients with PHG and acute bleeding episode). Patients were followed up for a mean of 36 months. Hemoglobin value was significantly improved after APC.

Also, these results were found to be closed to ***Abd El-Ghany et al. (2014)*** who reported that, the mean hemoglobin pre-APC was 8.3 ± 1.1 respectively which gradually elevated to become 10.72 ± 1.54, this elevation showed significance throughout treatment follow up.

Also These results were found to be close to ***Hanafy et al. (2016),*** who reported that a combination of APC and non-selective beta blockers was highly efficacious and safe in controlling bleeding from PHG. In addition, APC alone is rapid, and effective in the control of PHG induced bleeding, especially when beta blockers are contraindicated.

Also, these results were close to ***Hashim et al.(2017),*** who reported that, the mean hemoglboin pre-APC of was 7.82 ± 0.64 respectively which gradually elevated to become 9.92 ±.74, this elevation showed significance throughout treatment follow up.

A recent study, ***Herrera et al.(2008),*** has challenged the traditional consideration that lesions associated to PHG do not benefit from endoscopic therapy by evaluating the use of APC in treatment of PHG. In this study 11 patients with bleeding from PHG were included. APC sessions were aimed to ablate the greatest area of mucosal surface as possible, at least 80 % in diffuse lesions. Sessions were repeated every 2-4 weeks. The end point, which was defined by the absence of GIT bleeding or a reduction in transfusion requirements, was achieved in 81% of the patients who were bleeding from PHG.

In contrast, ***Orloff et al. (1994),***said that Portal gastropathy is not amenable to endoscopic therapy because of its diffuse nature and said that It is treated by reducing the portal hypertension pharmacologically with propranolol, radiologically with TIPS, or surgically with portosystemic shunt. Also ***Patwardhan et al. (2014)***, said that the treatment of PHG is aimed at reducing hepatic venous pressure gradients, most often by pharmacologic means, but may require shunt procedures in severe cases. On follow up endoscopy, recurrence of OV was observed in 7 patients, 4 patient had F1 and 3 patients had F2 without risk signs. There is evidence that EVL is associated with higher recurrence of varices after its eradication ***(Hou et al., 2000).*** As it dose not obliterate the deeper varices (the paraesophageal collaterals) and the feeder perforating veins running across the esophageal wall.

Also, EVL is not successful in prevention of esophageal varices recurrence because the basic physiological defect for development of OV which is the portal hypertension, remains unabated by EVL. Thus, EVL necessitates further sessions of EVL**,** or needs additional therapy to achieve complete mucosal fibrosis to prevent variceal recurrence ***(Triantos et al., 2014).***

PHG degree according to the NIEC was improved in 22 patients who showed mild degree of PHG out of the total number of the study group which was 30 patients. The endoscopic improvement was expected due to the superficial ablation of the ectatic and angiogenic vessels caused by the limited depth of coagulation.

There was no reported APC complication among the studied group of patients. This is in agreement with ***Abd El-Ghany et al.(2014), Hanafy et al. (2016)*** who reported that there were no complications related to APC.

Also this agreement with ***Hashim et al.(2017),***who reported that no APC complications among the studied groups of patients apart from mild gaseous distension and local pain at epigastrium although these effects are temporary and mild.

The lack of response in 8 patients can be attributed to, first is the possibility of the presence of deeply seated ectatic and angiogenic submucosal blood vessels which have not been adequately ablated by APC. Second is the fact that PHG is a hemodynamic condition and its aggravation by development of submucosal shunts is possible despite the treatment ***(Primignani et el., 2016).***

As regard the previously studied parameters (the hemoglobin level and the endoscopic degree of PHG) before and after applying APC, we found that APC is effective and safe method that can be used in treatment of severe degree of PHG, that considered a source of chronic blood loss.

Argon plasma coagulation (APC) is a new, efficacious, safe and easy to use method for the devitalization of tissue and hemostais. APC has been used successfully to treat vascular bleeding of upper digestive tract including gastric vascular ectesia (GAVE), PHG, sporadic angiodysplasia, hemorrhagic telengectesia and radiation induced enteropathy ***(Hanafy et al. 2016).***

CONCLUSION

1- Argon plasma coagulation is effective in achieving endoscopic hemostatic purposes in portal hypertensive gastropathy.
2- Multiple sessions of argon plasma coagualtion are needed to achieve complete and sustained endoscopic improvement of severe portal hypertensive gastropathy.
3- Argon plasma coagulation is a safe procedure with no obivious recorded complication.

REFERENCE

1. **Berzigotti, A., & Bosch, J. (2014).** Pharmacologic management of portal hypertension. *Clinics in liver disease*, *18*(2): 303-317.
2. **Biecker, E. (2013).** Portal hypertension and gastrointestinal bleeding: diagnosis, prevention and management. *World journal of gastroenterology: WJG*, *19*(31): 5035.
3. **Bosch, J., Groszmann, R. J., & Shah, V. H. (2015).** Evolution in the understanding of the pathophysiological basis of portal hypertension: How changes in paradigm are leading to successful new treatments. *Journal of hepatology*, *62*(1): S121-S130.

4. **Casas, M., Calvet, X., Vergara, M., Bella, M. R., Junquera, F., Martinez-Bauer, E., & Campo, R. (2015).** Lesiones vasculares gástricas en la cirrosis: gastropatía y ectasia vascular antral. *Gastroenterología y Hepatología*, *38*(2): 97-107.
5. **Colle, I., Verhelst, X., Geerts, A., & Van Vlierberghe, H. (2015).** Varices, portal hypertensive gastropathy and GAVE. *Cirrhosis: A practical guide to management*, 137.
6. **El-Ghany, S. M. A., El-taher, S. M., El-Zefzafy, W. M., & Sabal, A. A. (2014).** Safety and efficacy of endoscopic treatment with argon plasma coagulation of gastric bleeding in cases of gastric antral vascular ectasia and portal hypertensive gastropathy. *AAMJ*, *12*(1).
7. **Garcia-Tsao, G., Abraldes, J. G., Berzigotti, A., & Bosch, J. (2017).** Portal hypertensive bleeding in cirrhosis: risk stratification, diagnosis, and management: 2016 practice guidance by the American association for the study of liver diseases. *Hepatology*, *65*(65): 310-335.
8. **Gjeorgjievski, M., & Cappell, M. S. (2016).** Portal hypertensive gastropathy: A systematic review of the pathophysiology, clinical presentation, natural history and therapy. *World journal of hepatology*, *8*(4): 231.
9. **Gonzalez-Suarez, B., Monfort, D., Piqueras, M., Planella, M., Aracil, C., Gallego, A.,... & Balanzo, J. (2003).** Endoscopic treatment with argon plasma coagulation for portal hypertensive gastropathy with no response to pharmacological therapy. *Journal of Hepatology*, *38*: 59.
10. **Han, S., Chaudhary, N., & Wassef, W. (2015).** Portal hypertensive gastropathy and gastric antral vascular ectasia. *Current opinion in gastroenterology*, *31*(6): 506-512.
11. **Hanafy, A. S., & El Hawary, A. T. (2016).** Efficacy of argon plasma coagulation in the management of portal hypertensive gastropathy. *Endoscopy international open*, *4*(10): E1057-E1062.
12. **Haq, I., & Tripathi, D. (2017).** Recent advances in the management of variceal bleeding. *Gastroenterology Report*, *5*(2): 113-126.
13. **Hashim, A. E., Zaky, S., & Berengy, M. S. (2017).** Effect of Endoscopic Argon Plasma Coagulation on Gastrointestinal Blood Loss Due to Portal Hypertensive Gastropathy. *J Clin Gastroenterol Hepatol*, *1*, 2.
14. **Herrera, S., Bordas, J. M., Llach, J., Ginès, A., Pellisé, M., Fernández-Esparrach, G.,... & Castells, A. (2008).** The beneficial effects of argon plasma coagulation in the management of different types of gastric vascular ectasia lesions in patients admitted for GI hemorrhage. *Gastrointestinal endoscopy*, *68*(3): 440-446.
15. **Kovacs, T. O., & Jensen, D. M. (2002).** Recent advances in the endoscopic diagnosis and therapy of upper gastrointestinal, small intestinal, and colonic bleeding. *Medical Clinics of North America*, *86*(6): 1319-1356.
16. **Mokdad, A. A., Lopez, A. D., Shahraz, S., Lozano, R., Mokdad, A. H., Stanaway, J.,... & Naghavi, M. (2014).** Liver cirrhosis mortality in 187 countries between 1980 and 2010: a systematic analysis. *BMC medicine*, *12*(1): 145.
17. **Orloff, M. J., Bell, R. H., Orloff, M. S., Hardison, W. G., & Greenburg, A. G. (1994).** Prospective randomized trial of emergency portacaval shunt and emergency medical therapy in unselected cirrhotic patients with bleeding varices. *Hepatology*, *20*(4): 863-872.
18. **Parker, R. (2014).** Role of transjugular intrahepatic portosystemic shunt in the management of portal hypertension. *Clinics in liver disease*, *18*(2): 319-334.
19. **Patwardhan, V. R., & Cardenas, A. (2014).** Review article: the management of portal hypertensive gastropathy and gastric antral vascular ectasia in cirrhosis. *Alimentary pharmacology & therapeutics*, *40*(4): 354-362.
20. **Primignani, M., & Tosetti, G. (2016).** Portal hypertensive gastropathy after variceal eradication: more bleeding risk or just more reddening?
21. **Qamar, A. A., Grace, N. D., Groszmann, R. J., Garcia–Tsao, G., Bosch, J., Burroughs, A. K.,... & Garcia–Pagan, J. C. (2009).** Incidence, prevalence, and clinical significance of abnormal hematologic indices in compensated cirrhosis. *Clinical gastroenterology and hepatology*, *7*(6): 689-695.
22. **Qureshi, K., & Al-Osaimi, A. M. (2014).** Approach to the management of portal hypertensive gastropathy and gastric antral vascular ectasia. *Gastroenterology Clinics of North America*, *43*(4): 835-847.
23. **Rohmat, A. S., Makmun, D., & Hasan, I. (2014).** Gastric pH Comparison Between Mild and Severe Cirrhotic Portal Hypertensive Gastropathy. *The Indonesian Journal of Gastroenterology, Hepatology, and Digestive Endoscopy*, *15*(2): 78-82.
24. **Runyon, B. A. (2013).** Introduction to the revised American Association for the Study of Liver Diseases Practice Guideline management of adult patients with ascites due to cirrhosis 2012. *Hepatology*, *57*(4), 1651-1653.
25. **Salama, Z. A., Darweesh, S. K., Shehab, H. M., & Abd-Elhameed, M. A. (2016).** Etiology and prevalence of fatigue in chronic liver disease: clinical view. The Egyptian Journal of Internal Medicine, 28(2): 78.
26. **Satomi, E., Kaneko, A., Nishimura, Y., Michida, T., Komori, M., Iyoda, K.,... & Kato, M. (2000).** Effect of endoscopic treatment of gastric antral vascular extasia associated with chronic liver disease. *Digestive Endoscopy*, *12*(1): 25-28.
27. **Semenova, T. S., Pal'tseva, E. M., Zhigalova, S. B., & Shertsinger, A. G. (2014).** Portal

hypertensive gastropathy. *Arkhiv patologii*, *76*(6): 64-68.

28. **Tan, S., Wei, X., Song, M., Tao, J., Yang, Y., Khatoon, S.,... & Wu, B. (2014).** PUMA mediates ER stress-induced apoptosis in portal hypertensive gastropathy. *Cell death & disease*, *5*(3): e1128.
29. **Tjwa, E. T., Holster, I. L., & Kuipers, E. J. (2014).** Endoscopic management of nonvariceal, nonulcer upper gastrointestinal bleeding. *Gastroenterology Clinics of North America*, *43*(4): 707-719.
30. **Urrunaga, N. H., & Rockey, D. C. (2014).** Portal hypertensive gastropathy and colopathy. *Clinics in liver disease*, *18*(2): 389-406.