Zidan et al. Egyptian Liver Journal (2021) 11:8
https://doi.org/10.1186/s43066-021-00078-8

Egyptian Liver Journal

ORIGINAL RESEARCH ARTICLE Open Access

Bacteremia as a risk factor for variceal upper gastrointestinal tract bleeding in cirrhotic patients: a hospital-based study

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Abstract

Background: The presence of bacteremia as a complication of variceal bleeding in patients with liver cirrhosis had been investigated by many studies. The aim of this study was to assess the bacteremia as a risk factor for variceal upper gastrointestinal tract bleeding in cirrhotic patients. A cross-sectional study was conducted on 99 patients with chronic liver disease divided into three groups: group I included 35 patients presented with first attack of variceal bleeding, group II included 35 patients presented with recurrent attacks of variceal bleeding, and group III included 29 patients with no history of previous variceal bleeding as a control group. Routine laboratory tests were done, upper GI endoscopy, blood culture, and measurement of procalcitonin level in blood.

Results: Patients with recurrent variceal bleeding had statistically ($p < 0.05$) the highest percentage of positive blood culture followed by patients with first variceal bleeding and the control (60% vs 45.7% vs 24.1%) respectively. In addition to procalcitonin results, patients with recurrent variceal bleeding had statistically the highest values of PCT followed by patients with first variceal bleeding and the control (1.92 vs 0.325 vs 0.22 ng/ml) respectively. Multivariate regression analysis showed that procalcitonin and hemoglobin only was the significant predictors for variceal bleeding. Hemoglobin at cutoff value of ≤ 9.6 and procalcitonin (ng/dl) at cutoff value of > 1.76 is the most specific in predicting bleeding 86.21%, 86.21% (CI 95%) respectively.

Conclusion: Bacteremia and procalcitonin are risk factor for variceal bleeding in cirrhotic patients. Procalcitonin can be used as easily measurable and surrogate biomarker for bacteremia and variceal bleeding.

Keywords: Cirrhosis, PCT, Bacteremia, Variceal bleeding

Background

Liver cirrhosis is a chronic disease characterized by the presence of fibrosis and regeneration of nodules in the liver, whose consequences are the development of portal hypertension and liver failure. Liver cirrhosis is a public health and a worldwide problem. It affects all ethnic groups, ages, sex, and it is the cause of high rates of medical consultations, hospital admissions, health expenses, and morbidity and mortality [1]. Portal hypertension is one of the complications of liver cirrhosis and characterized by an increased portal pressure gradient leading to other consequences such as splenomegaly, growth of an extensive network of portal-systemic collaterals that shunt portal blood flow to the systemic circulation bypassing the liver, and development of a hyperkinetic circulatory state [2]. Upper gastrointestinal bleeding is a common medical emergency worldwide and refers to bleeding from the esophagus, stomach, or duodenum. Patients present with hematemesis or melena, although hematochezia can occur in the context of a major bleeding and it is typically associated with hemodynamic instability [3]. Variceal bleeding is the second most common cause of UGIB. Approximately,

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half the patients with cirrhosis have gastroesophageal varices as a consequence of portal hypertension. The severity of the underlying cirrhosis is directly related to the probability that the patient will have varices and signs of portal hypertension [4].

Bacterial infections in cirrhotic patients with UGIB are very common. Sepsis is the leading cause of hospitalization and death in intensive care units. Infections directly cause 30-50% deaths in patients with cirrhosis. The common bacterial infections in patients with cirrhosis include SBP, UTI, pneumonia, bacteremia, and soft-tissue infections [5]. Bacteremia is the presence of bacteria in the blood. The blood is normally a sterile environment, so the detection of bacteria in the blood is always abnormal [6]. Procalcitonin is an ideal marker for bacterial infection should allow an early diagnosis. Inform about the course and prognosis of the disease and facilitate therapeutic intervention. In comparison to other commonly used markers such as C-reactive protein, PCT has a superior diagnostic accuracy in distinguishing bacterial infection from non-infective causes of inflammation and from viral infections [7].

Table 1 Demographic and baseline characteristics of the study groups (n = 99)

	Group (I)		**Group (II)**		**Group (III)**		**Test**	***p***
	Patient with first attack of bleeding (n = 35)		**Patient with recurrent bleeding (n = 35)**		**Control patients (n = 29)**			
	No.	**%**	**No.**	**%**	**No.**	**%**		
Age (years)								
Mean ± SD	54 ± 9.6		53.7 ± 10.11		53.7 ± 9		***F***, 0.008	0.99
Sex								
Male	23	65.7%	19	54.3%	17	58.6%	χ^2, 0.965	0.78
Female	12	34.3%	16	45.7%	12	41.4%		
HE								
No	29	82.9%	25	71.4%	25	86.2%	χ^2, 5.25	0.26
Grade I	3	8.6%	2	5.7%	0	0%		
Grade II	3	8.6	8	22.9%	4	13.8%		
Ascites								
No	10	28.6%	4	11.4%	14	48.3%	χ^2, 17.13	**0.0088**
Minimal	4	11.4%	3	8.6%	0	0%		
Moderate	9	25.7%	15	42.9%	12	41.4%		
Severe	12	34.3 5	13	37.1%	3	10.3%		
Virology								
Negative	3	8.6%	3	8.6%	4	13.8%	χ^2, 3.85	0.42
HBV	2	5.7%	7	20%	4	13.8%		
HCV	30	85.7%	25	71.4%	21	72.4%		
	Group (I) Patient with first attack of bleeding (n = 35)		**Group (II) Patient with recurrent bleeding (n = 35)**		**Group (III) Control patients (n = 29)**		**Test**	***p***
WBC ($\times 10^3/mm^3$), *median (range)*	9.8 (3.3 – 12.8)		9.0 (1.7 – 14.5)		9.6 (4.3-12)		**KW**, 0.607	0.715
Hemoglobin (g/dl), *mean ± SD*	8.54 ± 1.96		8.35 ± 1.58		10.56 ± 1.11		***F***, 17.7	**< 0.001**
Platelet ($\times 10^3/mm^3$), *mean ± SD*	110.11 ± 39.9		86.17 ± 31.55		115.2 ± 23.6		***F***, 7.4	**0.001**
INR, *median (range)*	1.39(1.02-2.45)		1.65 (1.09-2.65)		1.22 (1.04-2.17)		**KW,** 17.8	**< 0.0001**
Creatinine (mg/dl), *median (range)*	0.99 (0.45-1.6)		0.98 (0.25-2.5)		0.77 (0.46-4.3)		**KW,** 2.79	0.247
Urea (mg/dl), *median (range)*	24 (11-66)		27 (14–82)		25 (13-32.2)		**KW,** 0.64	0.64
Albumin (g/dL), *mean ± SD*	2.8 ± 0.44		2.66 ± 0.61		2.98 ± 0.46		**F**, 2.91	**0.05**
Total bilirubin (mg/dl), *median (range)*	1.26 (0.3-4.4)		1.44 (0.59-35.3)		1.19 (0.51-30.9)		**KW**, 1.22	0.5
Direct bilirubin (mg/dl), *median (range)*	0.77 (0.11-2.99)		0.78 (0.12-30.57)		0.84 (0.16-20.8)		**KW**, 0.17	0.9
Spleen diameter (cm), *median (range)*	12 (9-16)		13.5 (10-16)		10.5 (10-11)		**KW**, 9.86	**< 0.001**
PV diameter (mm), *mean ± SD*	13.76 ± 0.5		13.78 ± 0.47		13.74 ± 0.47		***F***, 0.066	0.93

PCT increase is observed within 2-3 h. Levels then rise rapidly, reaching a plateau after 6-12 h. PCT concentrations remain high for 48 h, falling to their baseline value within the following 2 days. The half-life is about 20 to 24 h [8].

Previous clinical studies investigated the association of bacteremia and liver cirrhosis and its complications such as GI bleeding [9–13]. The aim of this study was to assess the bacteremia as a risk factor for variceal upper gastrointestinal tract bleeding in cirrhotic patients.

Methods

Study design

A hospital-based cross-sectional study was carried out in the gastroenterology and hepatology unit of Internal Medicine Department at the Faculty of Medicine, Zagazig University Hospitals. The Zagazig University institutional review board approved the study (ZU-IRB#5470-7-7-2019). Our study included 99 patients with chronic liver disease divided into three groups: the first group included 35 patients presented with the first attack of variceal bleeding, the second group included 35 patients presented with recurrent attacks of variceal bleeding and the third group included 29 patients with no history of previous variceal bleeding as a diseased control group. Written informed consent was obtained from all individual participants included in the study.

Patients selection and data collection

To be eligible for this study, the patient had to fulfill the following inclusion criteria: (1) patient aged 18 to 60 years old, (2) patient of both sexes with chronic liver disease with endoscopic evidence of upper GIT varices.

We excluded patient who had causes of bacterial infections (e.g., spontaneous bacterial peritonitis, chest infections, and urinary tract infections), patients who had received antibiotics within 1 week before admission, patients who had non-variceal causes of GIT bleeding including peptic ulcer disease, Mallory-Weiss tear, erosive gastritis or gastric cancer, and patients who had non-bacterial causes that may elevate PCT (false positive) including diseases (ESRD and vasculitis), drugs (IL-2, granulocyte transfusion), and stress as severe trauma and surgery. Eligible patients were subjected to history taking, full physical examination, and investigations to fulfill inclusion and exclusion criteria.

Laboratory determinations and clinical assessments

The following data were collected for each patient eligible for the study: age, gender, body mass index (BMI), residency, smoking status, hemoglobin A1C (HbA1C), fasting blood glucose (FBG), complete blood count (CBC), international normalized ratio (INR), total bilirubin, direct bilirubin, aspartate transferase (AST), alanine transferase (ALT), albumin, total plasma protein, alkaline phosphatase, creatinine, blood urea nitrogen (BUN), ESR, CRP, urine analysis, and ascitic fluid sample analysis (chemical, cellular and bacteriological). In addition, blood culture and serum procalcitonin measurement were done.

Abdominal ultrasonography (US) with Doppler for assessment of liver status, portal flow, portal vein and bipolar splenic size diameters, and upper GIT endoscopy (PENTAX EC-3890LK®) were performed by an experienced physician who was blinded to the clinical data of the patients.

Assessment procedures

Serum procalcitonin was measured by Cobas Integra e411 (Roche, Germany) at the clinical pathology department, Zagazig University Hospitals. The assay range:

Table 2 Comparison between studied groups regarding bacteremia and procalcitonin results (n = 99)

	Group (I)		Group (II)		Group (III)		Test	P
	Patient with first attack of bleeding (n = 35)		Patient with recurrent bleeding (n = 35)		Control patients (n = 29)			
	No.	%	No.	%	No.	%		
Blood culture								
Positive	16	45.7%	21	60%	7	24.1%	χ^2, 8.53	**0.001**
E.coli	10	28.6%	14	40%	4	13.8%		
Staph.	4	11.4%	5	14.3%	2	6.9%		
Klebseilla	2	5.7%	2	5.7%	1	3.4%		
Negative	19	54.3%	14	40%	22	75.9%		
Procalcitonin (ng/ml)								
Positive	15	42.9%	21	60%	6	20.7%	χ^2, 10.0	**0.006**
Negative	20	57.1%	14	40%	23	79.3%		
Procalcitonin (ng/ml), *median* (*range*)	0.325 (0.12-2.8)		1.92 (0.10-2.96)		0.22 (0.11-2.19)		**KW**, 7.422	**0.024**

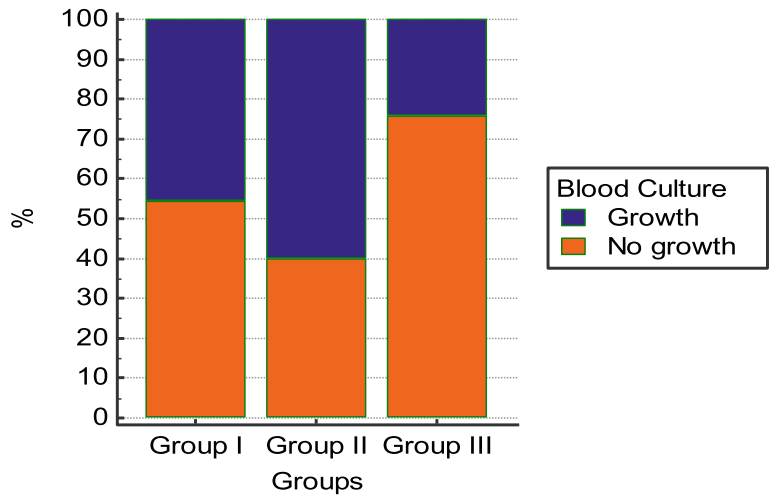

Fig. 1 Stacked bar chart showing blood culture among different studied groups

values < 0.5 ng/mL represent a low risk of severe sepsis and/or septic shock, and values > 2.0 ng/mL represent a high risk of severe sepsis and/or septic shock. Blood culture was done by using the BacT/ALERT Microbial Detection System. Then, subculture and antibiotic sensitivity by traditional methods. All other laboratory tests, including liver and renal function tests, and coagulation tests, underwent using the routine laboratory testing methods.

Statistical analysis

All statistical analysis was performed using the statistical software program, SPSS, for Windows version 25.0 (SPSS; Chicago, IL, USA). Categorical variables were presented in frequency and percentage, while numerical variables were presented with mean ± standard deviation (SD). Comparative analysis and inferential statistics were performed using parametric independent *t* test or Mann-Whitney *U* test was used for comparison according to the Gaussian distribution of the variables. For categorical variables, the chi-square test (or Fisher's exact test if appropriate) was used. For all statistical tests, *p* value ≤ 0.05 was considered statistically significant. Multivariate logistic regression analyses were used to determine the predictor variables for the variceal bleeding.

Results

A 99 CLD patients participated in the present study, of whom 35 patients presented with the first attack of variceal bleeding, 35 patients presented with recurrent attacks of variceal bleeding, whereas 29 patients with no history of previous variceal bleeding served as the control group. The demographic and baseline characteristics of the subjects based on the groups are presented in Table 1. The three groups were comparable in all demographics, baseline characteristics, and laboratory data. There was a statistically significant difference between studied groups regarding ascites, hemoglobin concentration, platelets, INR, albumin, and spleen diameter, $p < 0.05$.

Regarding blood culture and procalcitonin results, there was a statistically significant difference between the studied groups. *Escherichia coli* was the most common organism in blood culture-positive patients in the three groups, followed by *Staphylococcus auerus*, and the least prevalent organism was Klebsiella as were presented in Table 2. Patients with recurrent variceal bleeding had statistically ($p < 0.05$) the highest percentage of

Table 3 Procalcitonin in different blood culture results in the studied groups ($n = 99$)

	Blood culture				Test	*P*
	No growth ($n = 55$)		Growth ($n = 44$)			
	N	%	*N*	%		
Procalcitonin						
Negative	48	84.2%	9	15.8%	χ^2, 44.22	**< 0.0001**
Positive	7	16.7%	35	83.3%		
Procalcitonin (mg/dL), *median* (*range*)	0.22 (0.1–2.45)		2.1 (0.12-2.96)		**MW**, 5.99	**< 0.0001**

Table 4 Univariate and multivariate logistic regression analysis to determine predictors of bleeding in studied population (n = 99)

Variables	Coefficients β	Std. error	OR	P
Ascites	0.535	0.196	1.70	**0.0066**
Albumin (g/dL)	−1.006	0.491	0.365	**0.040**
Blood culture	1.259	0.495	3.52	**0.0110**
Procalcitonin (ng/ml)	0.772	0.271	2.16	**0.0045**
CTP	0.864	0.291	2.372	**0.003**
INR	2.911	0.881	18.384	**0.001**
Hemoglobin (g/dl)	−0.887	0.194	0.411	**< 0.0001**
Platelet ($\times 10^3/mm^3$)	−0.014	0.006	0.985	**0.030**
Procalcitonin (ng/ml)	0.96	0.35	2.61	**0.006**
Hemoglobin (g/dl)	−0.91	0.21	0.40	**< 0.0001**
Constant	8.51			

positive blood culture followed by patients with first variceal bleeding and the control (60% vs 45.7% vs 24.1%) respectively, as presented in Fig. 1.

In regarding procalcitonin results, patients with recurrent variceal bleeding had statistically the highest values of PCT followed by patients with first variceal bleeding and the control (1.92 vs 0.325 vs 0.22 ng/ml) respectively.

Statistically, patients with positive blood culture had a higher value of PCT while patients with negative blood culture had a low value of PCT (2.1 vs 0.22 ng/ml) respectively (Table 3).

In the univariate and multivariate logistic regression analysis model, high serum albumin was associated with reduced risk of bleeding (OR 0.365; 95% CI, 0.491-1.006, p = 0.040) while the other factors are associated with increased risk of bleeding. After adjusting the different parameters, procalcitonin, and hemoglobin only were the significant predictors for first or recurrent bleeding (OR 2.61; 95% CI, 0.35-0.96, p = 0.006) (OR 0.40; 95% CI, 0.21-0.91, p < 0.0001), respectively (Table 4).

The odds ratio of the first attack of bleeding among bacteremic patients is 2.65 times more than non-bacteremic patients. However, the odds ratio of recurrent gastrointestinal bleeding among bacteremic patients is 4.71 times more than non-bacteremic patients. Also, the odds ratio of the first attack of bleeding among procalcitonin positive patients is 2.87 times more than procalcitonin negative patients. However, the odds ratio of recurrent gastrointestinal bleeding among procalcitonin positive is 5.75 times more than procalcitonin negative patients (Table 5).

CTP score at cutoff value of > 6 is the most sensitive in predicting bleeding followed by hemoglobin at cutoff value of ≤ 9.6. While hemoglobin at cutoff value of ≤ 9.6 and procalcitonin (ng/dl) at cutoff value of > 1.76 is the most specific in predicting bleeding 86.21%, 86.21% (CI 95%) respectively (Table 6).

Our study illustrated that there was a significant difference between groups in *Child-Pugh score*, Child C presents in 40% of patients with the first attack of bleeding compared with 68.6 % in patients with recurrent bleeding and 27.6% of those without bleeding as in Table 7.

Discussion

Bacterial infections are common in patients with cirrhosis, which include spontaneous bacterial peritonitis, urinary tract infections, pneumonia, bacteremia, and soft-tissue infections. The incidence of bacteremia is increased in cirrhotic patients, as they are not only immunocompromised but also exhibit excessive activation of pro-inflammatory

Table 5 Assessment of bacteremia and positive procalcitonin as a risk for gastrointestinal bleeding among studied population (n = 99)

Blood culture	**Group (I) Patient with first attack of bleeding (n = 35)**		**Group (II) Patient with recurrent bleeding (n = 35)**		**Group (III) Control patients (n = 29)**	
	No.	**%**	**No.**	**%**	**No.**	**%**
Positive	16	45.7%	21	60%	7	24.1%
Negative	19	54.3%	14	40%	22	75.9%
Odds ratio (OR)	**2.65**					
			4.71			
Procalcitonin	**Group (I) Patient with first attack of bleeding (n = 35)**		**Group (II) Patient with Recurrent bleeding (n = 35)**		**Group (III) Control patients (n = 29)**	
	No.	**%**	**No.**	**%**	**No.**	**%**
Positive	15	42.9%	21	60%	6	20.7%
Negative	20	57.1%	14	40%	23	79.3%
Odds ratio (OR)	**2.87**					
			5.75			

Table 6 Specificity and sensitivity of different parameters in predicting esophageal bleeding (EVs) in our study (n = 99)

	Cutoff values	Sens. % (95% CI)	Spec. % (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)	AUC (95% CI)	*P*
Albumin (g/dL)	≤ 2.86	54.29%	75.86%	84.4%	40.7%	0.679	**0.0128**
Procalcitonin (ng/ml)	> 1.76	47.14%	86.21%	88.9%	40.3%	0.668	**0.0024**
Child score	> 6	85.71%	41.38%	77.9%	54.5%	0.680	**0.0023**
INR	> 1.38	65.71%	82.76%	90.2%	50%	0.484	˂ **0.0001**
Hemoglobin (g/dl)	≤ 9.6	84.29%	86.21%	93.7%	69.4%	0.895	˂ **0.0001**

cytokines and are thus prone to infections [5]. Procalcitonin (PCT) is used as a biomarker for the diagnosis of bacteremia, sepsis, and septic shock [14].

On univariate analysis, hemoglobin level was a good predictor for variceal bleeding and bacteremia. Also, albumin level was a good predictor for variceal bleeding and bacteremia. So increased hemoglobin and albumin are associated with reduced risk of bleeding but positive blood cultures, ascites, etc. are associated with increased risk of bleeding.

These results are parallel with Kothari and colleagues who showed that hemoglobin level is lower in the bleeding esophageal varices group (8.26 ± 2.25) than the non-bleeding group (8.93 ± 2.37) [15]. Grothaus and his colleagues also reported similar results that patients with bleeding events after EVL had significantly lower hemoglobin levels [16].

Regarding platelet counts, there was a statistically significant difference between the studied groups and it was a significant predictor for variceal bleeding. This is consistent with Kothari et al. who showed that platelet count is lower in the esophageal varices bleeding group than the non-bleeding group. Cut off 134 × 103/mm3 was significant predictor of variceal bleeding (sensitivity = 80.33, specificity = 62.41, OR = 6.77) [15]. Giannini et al. and Schepis et al. who reported that a platelet count of less than 100,000 can be used as a predictor of variceal bleeding, and of less than 90,000 is associated with an increased risk of having variceal bleeding by nearly 2.5-folds [17, 18].

Bacteremia increased the risk of the first attack of variceal bleeding by 2.65 times more than non-bacteremic patients and increased the risk of recurrent bleeding 4.71 times more than non-bacteremic patients. Our results showed *E. coli* was the most common organism in blood culture-positive patients in the bleeding and non-bleeding groups, followed by *Staph. aureus*, and the least prevalent organism was Klebsiella. This is consistent with Bunchorntavakul and Chavalithamrong who showed that the major causative organisms are gram-negative bacteria, e.g., *E. coli*, *Klebsiella spp.* and *Enterobacter spp.*, whereas gram-positive bacteria, especially *Enterococci* and *Staphylococcus aureus*, comprise about 20% and anaerobes only 3% [19]. In addition, Guarner et al. had reported that bacteremia presents more frequently in patients with variceal bleeding [20].

Our results demonstrated that median procalcitonin levels were significantly higher in both bleeding groups than the control group and its level was higher in patient with recurrent bleeding than the first attack of bleeding. Our results agree with Juutilainen et al., who showed that, with the cutoff value for PCT level set to 0.5 ng/ml, diagnostic sensitivity to bacterial infection was 65%, and specificity was 96%. Additionally, at serum PCT levels higher than 1.2 ng/ml, sensitivity reaches 100% [21].

In addition, these results are consistent with the findings of Neofytos and his colleagues [22]. Lee SH et al. reported that leukocytes, induced by inflammatory response, produce excessive amounts of pro-inflammatory cytokines, such as interleukins 1, 6, and 8 and tumor necrosis factor-α which induce the production of PCT that expressed by nearly all kinds of parenchymal cells [23].

Table 7 Severity of liver disease in studied population (n = 99)

	Group (I)		Group (II)		Group (III)		*P*
	Patient with first attack of bleeding (n = 35)		Patient with recurrent bleeding (n = 35)		Control patients (n = 29)		
	No.	%	No.	%	No.	%	
CTP score, *median* (*range*)	9 (5-12)		10 (5-14)		8 (5-13)		**0.002**
CTP class							
A	8	22.9%	2	5.7%	12	41.4%	**0.003**
B	13	37.1%	9	25.7%	9	31.0%	
C	14	40%	24	68.6%	8	27.6%	

Conclusion

Our study revealed that bacteremia and high procalcitonin level are risk factor variceal upper GI bleeding in cirrhotic patients. Procalcitonin can be used as an easily measurable and surrogate biomarker for bacteremia and variceal bleeding in cirrhotic patients even absence of leukocytosis. Further studies with large sample size are needed for more illustration of our study's results.

Abbreviations

ALT: Alanine aminotransferase; AST: Aspartate transferase; BMI: Body mass index; BUN: Blood urea nitrogen; CLD: Chronic liver disease; FBG: Fasting blood glucose; INR: International normalized ratio; HbA1C: Hemoglobin A1C; UGIB: Upper gastrointestinal bleeding; PCT: Procalcitonin

Acknowledgements

The authors would like to thank all patients for their participation in this research.

Authors' contributions

SZ generated the research idea, MZ and WM performed the clinical examination, HS performed the laboratory analysis, and AG wrote the largest part of the manuscript. All authors shared in analyzing and interpreting the patient data and in writing the manuscript. All authors read and approved the final manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The Zagazig University institutional review board approved the study (ZU-IRB#5470-7-7-2019). Written informed consent was obtained from all individual participants in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Received: 10 October 2020 Accepted: 7 January 2021
Published online: 25 January 2021

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