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Original Research Article

Role of arginase 1 immunohistochemical marker in differentiating hepatocellular carcinoma from other primary and secondary carcinomas of the liver, a tissue microarray study

Dina H Elzeftawy[1], Ibrahim M Elshawaf[1], Wagdi F Elkashef[1], Shaimaa M Yussif[1,*]

[1] *Dept. of Pathology, Faculty of Medicine, Mansoura University, Egypt*

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ABSTRACT

Background and Objectives: Hepatocellular carcinoma (HCC) is the most prevalent type of primary cancer of the liver in adults represent about 80%-90% of all liver cancers. It is essential to differentiate primary HCC and intrahepatic cholangiocarcinoma and metastatic carcinoma. Arginase-1 was considered as the most sensitive and specific marker of benign and malignant hepatocyte. This study aimed to detect the diagnostic role of immunohistochemical expression of arginase-1 in differentiating HCC From cholangiocarcinoma and metastatic carcinomas of the liver in comparison with hepatocyte paraffin antigen -1 (HepPar-1) and Glypican 3.

Materials and Methods: This is a retrospective study was performed on 117 cases, 77 cases were diagnosed as HCC, 13 cases as cholangiocarcinoma and 27 cases as metastatic carcinomas in the liver. Cases obtained from surgical pathology laboratory at Gastroenterology Center, Mansoura University, Egypt during the period from 2014 to 2017. All the studied cases were immunostained with Arginase 1, Heppar 1and Glypican 3.

Results: Arginase 1 was expressed in all 77 HCC cases with sensitivity (100%), while Arginase 1 was expressed only in 1 cholangiocarcinoma case and negative in other metastatic carcinomas with specificity(97.5%), the overall accuracy was (99.1%). On the other side, Glypican 3 was expressed in 36 out of 77 HCC cases with sensitivity (46.8%), while Glypican 3 was expressed in 3 out of 40 cholangiocarcinoma and other metastatic carcinomas with specificity (92.3%), overall accuracy (62.4%). Heppar 1 was expressed in 69 out of 77 HCC cases with sensitivity (89.6%), while Heppar 1 was negative in all cholangiocarcinoma cases and other metastatic carcinomas with specificity (100%). The overall accuracy was 93.2%.

Discussion and Conclusion: Arginase 1 is the most sensitive and accurate marker in differentiating HCC from non HCC cases in liver, while heppar is most specific and second accurate marker in differentiating HCC from cholangiocarcinoma and metastatic carcinomas in the liver. Arginase-1 and HepPar-1, are the best markers regarding sensitivity and specificity for small liver biopsies.

1. Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer. Globally, it is the fifth most common cancer and the second leading cause of cancer related death.[1]

Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) infections and alcoholism are the most important etiological factors of HCC as they result in cirrhosis which is

* *Corresponding author*.
E-mail address: shimo.yussif@gmail.com (S. M. Yussif).

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considered a major predisposing factor of HCC.[2] In Egypt, there was a remarkable increase in the proportion of HCC among patients with chronic liver diseases due to the high burden of chronic hepatitis C virus (HCV) infection.[3]

The distinction between a primary HCC and intrahepatic cholangiocarcinoma and metastatic carcinoma is essential, as they are different in treatment strategies.[4] The immunohistochemical markers available for distinguishing HCC from cholangiocarcinoma and metastatic carcinoma are of a limited number. The traditional immunohistochemical marker of HCC is alpha-fetoprotein, Polyclonal carcinoembryonic antigen and CD10.[5]

HepPar-1 (hepatocyte paraffin antibody) is one of the most reliable markers for hepatocellular differentiation, but usually of low sensitivity in poorly differentiated HCC. HepPar-1 is typically negative in most adenocarcinomas but may occasionly show strong cytoplasmic expression in some gastric, esophageal, and pulmonary adenocarcinomas.[6]

Glypican-3 is considered also a good immunohistochemical marker in diagnosis of HCC although not expressed in normal liver. Expression of Glypican-3 is detected in 64% to 90% of HCC. It is more commonly positive in poorly differentiated HCC, so it has the advantage in distinguishing poorly differentiated HCC from adenocarcinoma. However, some tumors may express Glypican-3 such as germ cell tumors, pulmonary squamous cell carcinoma, and occasionally gastric adenocarcinomas.[4]

Arginase-1 has been considered as a useful immunohistochemical marker in the diagnosis of primary HCC and also in differentiating this from non-HCC. Arginase 1 is valuable as a sensitive and specific marker of benign and malignant hepatocytes.[7] In normal liver tissue, Arginase -1 is expressed as strong, diffuse cytoplasmic reactivity (not granular as that of HepPar-1). Cytoplasmic reactivity may be occasionly associated with patchy nuclear reactivity. Arginase 1 is negative in sinusoidal endothelial cells, bile duct epithelial cells, Kupffer cells and vascular endothelial cells.[7]

This study aims to asses immunohistochemical expression of arginase-1 in HCC cases, cholangiocarcinoma and metastatic carcinoma involving the liver in comparison with HepPar-1 and Glypican 3. This study help to stratify the role and efficacy of arginase-1 in the diagnosis and differentiation of these tumors & calculating the sensitivity and specificity through positive and negative predictive values of Arginase-1 immunohistochemistry.

2. Materials and Methods

This retrospective study was performed on 77 cases of HCC, 13 cases of cholangiocarcinoma and 27 cases of metastatic carcinomas in the liver. These cases were collected from surgical pathology laboratory at Gastroenterology Center, Mansoura University, Egypt during the period from 2014 to 2017. The clinicopathological data were retrived. Revision of Heamatoxylin and eosin (Hx&E) slides was done to confirm the diagnosis. This study was approved by Institutional Research Board (IRB) at Faculty of Medicine, Mansoura University, Egypt. Tissue microarray (TMA) was assembled manually made by a mechanical pencil tip of 0.7 mm.

2.1. Immunohistochemical staining and scoring

Tissue sections were cut at thickness of 4 μm. After that, deparaffanize, rehydrate and epitope retrieve. The preferred method was the use of Heat Induced Epitope Retrieval (HIER) technique using Cell Marque triology in conjunction with a pressure cooker. Upon completion, rinse with phosphate-buffered saline (PBS). Antigen retrieval done by heating in citrate buffer PH(6.0). Endogenous peroxidase activity was blocked by 3% hydrogen peroxide. Then we incubate the tissue sections with antibodies against both Heppar-1 and Glypican 3 (mouse monoclonal, Ig G, Arcadia, USA) and Arginase-1(rabbit polyclonal, Ig G, Gene Tex, Inc. North America, GTX 113131) for 60 minutes.

Antibodies were diluted at 1:100 in PBS. Then, Incubate with UltraVision One HRP Polymer (Thermoscientific, USA) for 30 min at room temperature, wash 4 times in buffer solution. Then DAB was used as Chromogen. Then tissue sections were counterstained with hematoxylin, dehydrated using ascending grades of alcohol and mounted using mounting medium and cover with cover slide.

2.2. Interpretation of immunohistochemical staining results

Scoring of IHC results was done by two pathologists. A score was calculated include both intensity and percentage of stained cells.[6]

For Arginase 1, only cytoplasmic or nuclear and cytoplasmic expression in at least 5% of cells was considered as positive. Regarding Heppar-1 staining, granular cytoplasmic expression in at least 5% of cells was considered as positive, while for Glypican -3 staining, cytoplasmic and/or membranous expression in at least 5% of cells was considered as positive. The staining intensity was scored as (0 for no staining, 1+ for weak staining, 2+ for moderate staining, and 3+ for strong staining. The percentage of positive tumor cells was recorded as focal= 1 (<10%), patchy= 2(10–50%), or diffuse= 3 (>50%).[1]

Percentage of positive tumor cells scored as: 0 (no reactivity) or less than 5% staining, + 1 (5%-10% staining), +2 (10%-50% staining), or +3 (>50% staining).[6]

2.3. Statistical analysis and data interpretation

Data were tabulated and analyzed using IBM SPSS Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp. Qualitative data were described using number and percent. Quantitative data were described using median (minimum and maximum) for non-parametric data and mean, standard deviation for parametric data after testing normality using Kolmogrov-Smirnov test. Significance of the obtained results was judged at the (0.05) level.

3. Results

This study was performed on 117 cases, 77 cases (65.8%) were diagnosed as hepatocellular carcinoma, 13 cases were cholangiocarcinoma and 27 cases (34.2%) were metastatic carcinomas in the liver. The studied cases were collected from surgical pathology lab at Gastroenterology Center, Mansoura University, Egypt during the period from 2014 to 2017. Tissue specimens from HCC and metastatic tumor tissues were taken from the patients who underwent partial hepatectomy.

3.1. Arginase 1 protein expression in studied HCC cases and Non HCC cases

Table 1: Arginase 1 protein expression in the studied HCC cases

Arginase 1	Number	Percentage(%)
Positive (score+1)	10	13
Positive (score+2)	36	46.8
Positive (score +3)	31	40.3

Positive Arginase 1 expression was detected in all 77 (100%) of HCC cases, 10 cases (13%) revealed mild positive nuclear and /or cytoplasmic staining (score 1), 36 cases (46.8%) revealed moderate positive cytoplasmic and /or nuclear staining (score 2), 31 cases (40.3%) revealed strong positive nuclear and /or cytoplasmic staining (score 3) (Table 1)(Figure 1).

In the studied Non HCC cases, Arginase 1 protein expression was positive in only 1 case (2.5%) diagnosed as cholangiocarcinomas and negative in other 39 cases (97.5%)(Figure 2).

3.2. Heppar 1 protein expression in studied HCC and Non HCC cases

As shown in Table 2, Heppar 1 was positive in 69 (89.7%) of HCC cases, of which 9 cases (13%) revealed mild positive granular cytoplasmic staining (score 1)(Figure 1), 29 cases (42%) revealed moderate positive granular cytoplasmic staining (score 2), 31 cases (45%) revealed strong positive granular cytoplasmic staining (score 3), while only 8 (10.3%) HCC cases were negative for Heppar staining. In

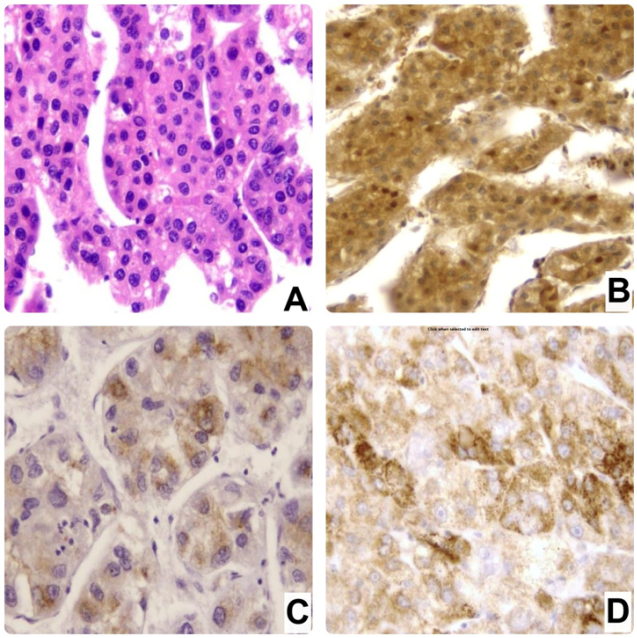

Fig. 1: Acase of grade II HCC trabecular pattern.(Hx&E x400)(**A**): Arginase staining, cytoplasmic and focal nuclear, score +3 (IHC x200); (**B**): Glypican 3 staining, cytoplasmic, score +1 (IHCx400); (**C**): Heppar 1 staining, cytoplasmic granular, score +1 (IHCx400).(**D**)

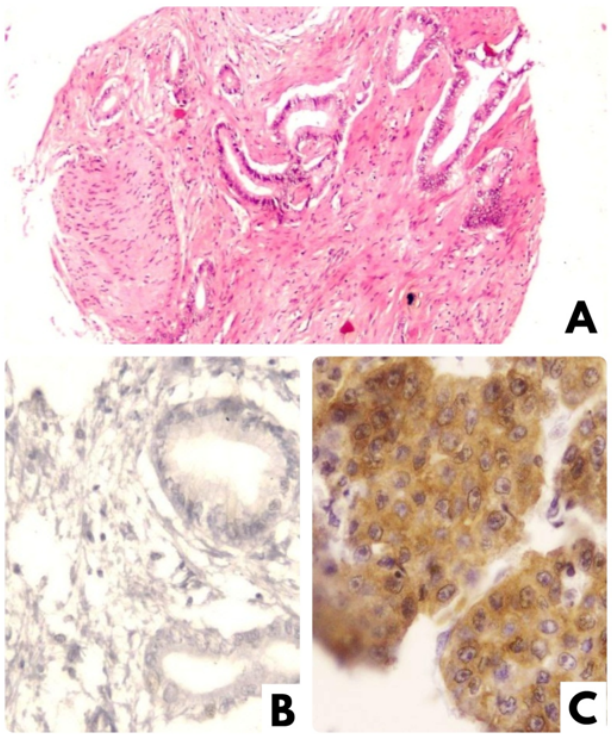

Fig. 2: A case of cholangiocarcinoma with excessive desmoplasia and perineural invasion. (Hx&E x200); (**A**): Negative Arginase 1 staining (IHC x400); (**B**): Positive Glypican 3 cytoplasmic staining (IHC x400)(**C**)

Table 2: Heppar 1 protein expression in studied HCC cases

Heppar 1	Number	Percentage(%)
Negative	8	10.3
Positive (score +1)	9	11.7
Positive (score+2)	29	37.7
Positive (score+3)	31	40.3

the studied non HCC cases: Heppar 1 was negative in all cholangiocarcinomas and metastatic cases (100%).

3.3. Glypican 3 protein expression in studied HCC and non HCC cases

Table 3: Glypican 3 protein expression in the studied HCC and non HCC cases

Glypican 3 in HCC cases	Number	Percentage (%)
Negative (zero)	41	53.2
Positive (score+1)	10	27.7
Positive (score +2)	16	44.4
Positive (score +3)	10	27.7
Glypican 3 in non HCC cases		
Negative	37	92.5
Positive	3	7.5

As shown in Table 3; Positive Glypican 3 expression was detected in 36 (46.7%) of HCC cases, of which 10 cases (27.7%) revealed mild positive membranous and/or cytoplasmic staining (score 1)(Figure 1), 16 cases (44.4%) revealed moderate positive membranous and/or cytoplasmic staining (score 2), 10 cases (27.7%) revealed strong positive membranous and/or cytoplasmic staining (score 3), while 41 (53.2%) of HCC cases were negative for glypican staining. Positive Glypican 3 expression was detected in 3 (7.5%) cases out of the studied 40 Non HCC cases: Two cases were diagnosed as Cholangiocarcinomas and 1 case diagnosed as metastatic adenocarcinoma (Figure 2). 37 cases (92.5%) were negative for glypican 3 expression (Table 3).

3.4. Validity of the three studied markers in differentiating HCC from Non HCC

As shown in Table 4; Arginase 1 expression detected in all 77 HCC cases with sensitivity 100%, while Arginase 1 expression was detected in only 1 cholangiocarcinoma case and negative in other metastatic cases with specificity 97.5%, the overall accuracy was about 99.1%.

On the other side, Glypican 3 was positive in 36 out of 77 HCC cases with sensitivity 46.8%, while Glypican 3 was positive in 3 out of 40 Cholangiocarcinoma and other metastatic cases with specificity 92.3%, the overall accuracy was about 62.4%.

However, Heppar 1 expression was detected in 69 out of 77 HCC cases with sensitivity 89.6%.

While Heppar 1 expression was negative in all Cholangiocarcinoma and other metastatic cases with specificity 100%, the overall accuracy was about 93.2%.

3.5. Validity of the three biomarker in differentiating HCC grades

As shown in Table 5 which describe the validity of the three markers in relation to different tumor grades of HCC. Arginase-1 expression was positive in all HCC cases (100%) in different tumor grades. HepPar-1 was positive in all 17 cases (100%) of well-differentiated HCC; however, HepPar-1 was only positive in 36 of 38 (94.7%) moderately differentiated HCC cases and 16 of 22 cases (72.7%) poorly differentiated HCC. In contrast, glypican 3 was positive in 7 of 17 cases (41.2%) of well differentiated HCC, and in 15 of 38 cases (39.5%) of moderately differentiated HCC and 14 of 22 cases (63.6%) of poorly differentiated HCC.

4. Discussion

In the present study, Arginase 1 expression was positive in all studied 77 HCC cases (100%), while Heppar 1 expression was positive in 69 out of 77 HCC cases (89.7%); however Glypican 3 expression was positive in 36 out of 77 studied cases (46.4%). All cases that show positive HepPar-1 expression is associated with positive arginase-1 expression.

In addition, a more diffuse pattern of staining is observed with arginase-1 in HCC cases than HepPar-1 and Glypican 3. This facilitates the interpretation of Arginase particullarly in small liver biopsies.

In agreement with current results, several studies reported that Arginase 1 was most sensitive IHC marker with higher rates ranging (95-100%) in diagnosis HCC compared to Heppar 1 and Glypican 3. However, some other studies reported that Arginase was most sensitive IHC marker with relatively lower rates ranging (80-90%). One study reported Arginase sensitivity about 96% compared to Heppar sensitivity (84%). As well as others reported Arginase sensitivity about 81% compared to heppar sensitivity (70%) and Glypican sensitivity (54%).[5,6]

Also, Sang et al. with Arginase sensitivity about (96%) compared to heppar sensitivity (80.7%)[8] and McKnight et al with Arginase sensitivity about 84% compared to heppar sensitivity (73%) and Glypican sensitivity (57%).[9]

In contrast to current result, one reported study showed immunoreactivity of Arginase 1 in 29 HCC cases. This study was performed on FNAC. They reported that Heppar 1 is more sensitive than Arginase 1. Positive Arginase expression was detected in 23 cases with sensitivity about (79%) compared to Heppar positivity in 24 cases with sensitivity (83%) and Glypican positivity in 25 cases with

Table 4: Validity of the studied three markers in differentiating HCC from non HCC

Arginase 1	HCC	Metastasis	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Negative	0	39	100.0	97.5	100.0	98.7	99.1
Positive	77	1					
Heppar 1							
Negative	8	40	89.6	100.0	100.0	83.3	93.2
Positive	69	0					
Glypican 3							
Negative	41	37	46.8	92.5	92.3	47.4	62.4
Positive	36	3					

Table 5: Arginase 1, Heppar 1, Glypican 3 expression in well, moderate, poorly differentiated HCC

Biomarkers	Well differentiated HCC (N=17)	Moderately Differentiated HCC (N=38)	Poorly differentiated HCC (No=22)	P value
Arginase 1	17 (100%)	38 (100%)	22 (100%)	1.0
Heppar 1	17 (100%)	36 (94.7%)	16 (72.7%)	0.007*
Glypican 3	7 (41.2%)	15 (39.5%)	14 (63.6%)	0.017*

MC: Monte Carlo test, *statistically significant (if p<0.05)

sensitivity (86%) in fine needle cytology.[10] Although in TMA 17 out of 18 HCC cases were positive for Arginase1 with sensitivity (94%). The sensitivity on FNA samples may be low because of the small number of cases in this study (n = 29) and the limited number of tumor cells available compared with the surgical case.[10]

Regarding non HCC cases, in the current study, histologically 13 tumors proved to be Cholangiocarcinoma, other 27 cases were metastatic adenocarcinomas infiltrating liver without knowing the primary tumor origin.

Twelve out of 13 cholangiocarcinoma cases and 27 metastatic adenocarcinoma cases were negative for Arginase-1 with only 1 cholangiocarcinoma case was positive for arginase 1 (2.5%) with specificity (97.5%). Although, 40 out of 40 non HCC studied cases were negative for Heppar 1 with specificity about (100%). However, 37 out of 40 non HCC cases were negative for Glypican 3 with specificity about (92.5%).

These results indicate higher specificity of Arginase 1 by about (97.5%) in differentiating HCC from non HCC, except for 1 case of Cholangiocarcinoma was positive. This occasional positivity may be explained by the fact that HCC and CC have a common progenitor cell.

This was also detected by one study which concluded that arginase-1 was expressed in high percentage in hilar and peripheral intrahepatic CC. Arginase-1 was positive in 78% of intrahepatic cholangiocarcinomas. But their results were not clear or intensified by other studies or experience.[11]

Our results were also confirmed by other studies that support negativity of Arginase1 in metastatic adenocarcinoma, that concluded arginase specificity (100%) compared to Heppar specificity (97.4%) and Glypican specificity (96.7%). Others concluded that Arginase1 specificity (100%) compared to Heppar specificity (87%).[10,12]

Arginase-1 is a part of the urea cycle only in the liver, however positive Arginase-1 expression was rarely demonstrated in adenocarcinomas of the pancreas, prostate, colon, and breast. Usually staining pattern in positive cases was focal and weak.[1]

On the other hand, some studies showed that arginase-1 can be positive in adenocarcinomas, especially of pancreatic origin and not ultimately specific for hepatic differentiation.[13]

Radwan and Ahmed found that Arginase 1 was positivein 1 out of 38 metastatic adenocarcinoma cases (pancreatic origin) with arginase 1 specificity (96%) compared to Heppar specificity (84%).[4] In addition, some studies demonstrated arginase-1 immunohistochemical expression was expressed at high levels in the liver and at moderate levels in the pancreas in rats.[14]

In the current study, no Heppar 1 expression was detected in all 40 Non HCC and metastatic cases with specificity (100%). Fujiwara et al., also found that Heppar 1 specificity (95%) with superiority over Arginase 1 specificity (90%).[6]

In contrast to the results of current study regarding Heppar 1 in non HCC and metastatic adenocarcinoma cases, some studies found that Heppar 1 expression has detected in different neoplasms, especially in adenocarcinoma of stomach (12-47%), esophagus(20%), gall bladder(25%), pancreas(10%), Cholangiocarcinoma (30%), lung (24%), adrenocortical carcinomas(20%).[14]

HepPar 1 was positive in 6 cases of metastatic carcinoma (from colon and stomach).[4] Moreover, Yan et al. also detected HepPar-1 reactivity in 2 colonic adenomas, 8 colonic adenocarcinomas, 2 pulmonary adenocarcinomas, 1 chromophobe RCC, and 9 gastric adenocarcinomas (47.4% of cases).[5]

In this study results, Glypican 3 show positive reaction in 3 out of 40 Non HCC cases with specificity (92%) while Arginase 1 specificity (97.5%) and Heppar1 specificity was (100%).

These results go hand in hand with other studies that detect Glypican 3 specificity about (92%)[6] and (96%).[10]

As glypican 3 expression was repoted in other tumors, as ovarian carcinomas (all subtypes), especially clear cell carcinomas (17% to 64%), renal cell carcinomas, (clear cell type (2% to 5%), papillary type (4% to 26%), and chromophobe type (20% to 80%).[15] It also has been detected in adenocarcinomas of the stomach (9% to 20%), lung (7% to 10%), Cholangiocarcinoma (2% to 10%), squamous cell carcinomas of the esophagus (25%), lung (13% to 55%), and larynx (13%), melanomas (30%), and some germ cell tumors, particularly yolk sac tumors (100%) and choriocarcinomas (85%).[15]

In comparison with glypican 3, arginase-1, is more sensitive for hepatocellular carcinomas. Although Glypican 3 is negative in benign hepatocellular lesions, it is more valuable than arginase-1 in the differential diagnosis of benign and malignant hepatocellular lesions especially in proplematic cases.[14]

Arginase-1 is rarely expressed in non-hepatocellular tumors; In comparison with glypican 3, its specificity has the prevalage to differentiate between hepatocellular carcinomas and non-hepatocellular neoplasms.[14]

5. Conclusion

Arginase-1 is the most sensitive marker of hepatic differentiation and can be easily applied and interpreted in small biopsies. However, arginase-1 staining can be observed in cholangiocarcinoma so is not totally specific.

Using arginase-1 and HepPar-1 together are the best coupled markers regarding percentages of sensitivity and specificity in liver biopsies.

Although Glypican 3 lacks specificity, it is not expressed in benign hepatocellular lesions, and this is an advantage of it over Arginase 1 and Heppar.

6. Source of Funding

None.

7. Conflict of Interest

None.

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Author biography

Dina H Elzeftawy, Dina Elzeftawey https://orcid.org/0000-0003-3673-8173

Ibrahim M Elshawaf, Professor

Wagdi F Elkashef, Professor https://orcid.org/0000-0003-2600-8003

Shaimaa M Yussif, Assistant Professor https://orcid.org/0000-0001-6041-3702

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