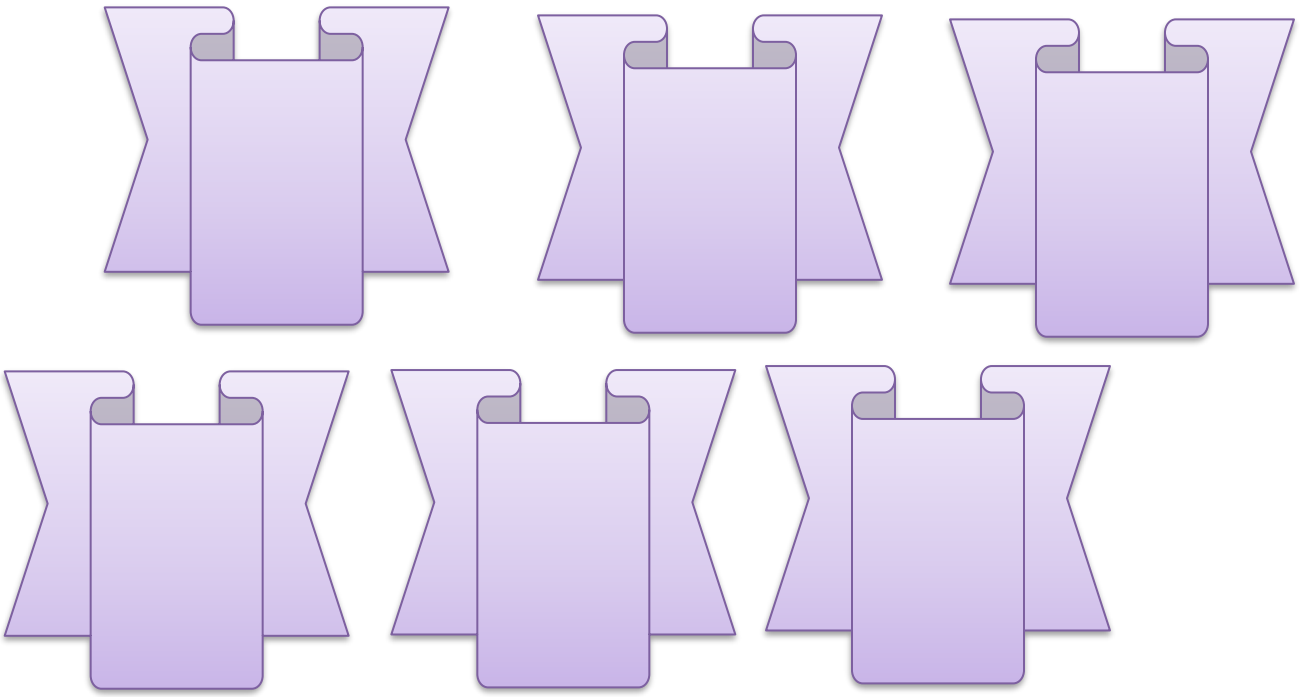
International Journal of Medical Arts

Volume 5, Issue 6, June 2023

https://ijma.journals.ekb.eg/



Print ISSN: 2636-4174

Online ISSN: 2682-3780

Available online at Journal Website
https://ijma.journals.ekb.eg/
Main Subject [Clinical Pathology]

Original Article

Evaluation of Progranulin Serum Levels in Egyptian Adults De Novo Acute Myeloid Leukemia Patients

Muhammad R. Abd El Aziz Askar *[1], Nagwa M. Abd El Moneim Mowafy [2], Mahmoud Abd El Latif Hashsih [2]

[1] Department of Clinical Pathology, Maadi Military Hospital, Egyptian Armed Forces, Cairo, Egypt
[2] Department of Clinical Pathology, Faculty of Medicine, Al-Azhar University, Cairo, Egypt

Article information

Received: 06-03-2023

Accepted: 15-06-2023

DOI: 10.21608/IJMA.2023.198266.1635.

*Corresponding author

Email: egyptianaskar@gmail.com

Citation: Askar MRA, Mowafy NMA, Hashsih MA. Evaluation of Progranulin Serum Levels in Egyptian Adults De Novo Acute Myeloid Leukemia Patients. IJMA 2023 June; 5 [6]: 3311-3316. doi: 10.21608/IJMA.2023.198266.1635.

ABSTRACT

Background: Various cancer cells share critical physiologic changes that promote malignant development. Progranulin [PGRN], a growth factor, has major biological impact on several cancer types.

Aim of the work: To measure levels of progranulin in the serum of adult patients with acute myeloid leukemia [AML] before and after treatment. Next, to correlate their serum levels to prognosis.

Patients and Methods: Our prospective observational study was conducted on 40 adult patients with AML recruited from Clinical Hematology and Oncology hospital in Maadi Military Complex before and after chemotherapy treatment during six months. 15 adult healthy people with comparable age and sex were subjected as a control group. The patients received conventional chemo-therapy protocols according to NCCN guidelines for AML treatment. Either routine laboratory investigations or disease-specific labs were performed. Progranulin level in serum was assessed using ELISA.

Results: Serum Progranulin levels are significantly higher for AML patients than control group. There is statistically insignificant difference of serum Progranulin levels after chemotherapy treatment compared to its level at diagnosis among AML patients.

Conclusion: Our investigation has led us to the conclusion that adult AML patients have elevated PGRN levels, which may be related to the tumor burden in these individuals.

Keywords: Progranulin; Chemotherapy; AML; Cancer.

INTRODUCTION

The regulatory systems that typically regulate cell proliferation and homeostasis are flawed in cancer cells. Various cancer cells share critical physiologic changes that promote malignant development. Progranulin [PGRN], a growth factor, has major biological impact on several cancer types. Due to its triggering of cell multiplication, motility, incursion, angiogenesis, oncogenic action, resistance to anticancer treatments, and immune evasion, this protein regulates carcinogenesis [1].

Breast, ovarian, prostate, bladder, and liver cancers were among the tumors where PGRN played tumorigenic functions; higher levels of PGRN expression in tumors were associated with a worse prognosis [2]. PGRN attaches to receptors in the extracellular matrix, which either activates a signal transduction pathway or causes the cell to take it up. PGRN has been implicated in the binding of SORT1, which enhances tumor cell survival, migration, and proliferation and results in treatment resistance, according to a series of studies [3].

Furthermore, PGRN might promote the development of the tumor stroma. Additional investigations revealed that progranulin may be facilitated by tumor necrosis factor and EPH receptor A2 [4]. It is thought that PGRN functions as a neurotrophic factor in corticogenesis. According to recent research, progranulin may play a role in controlling the early development of cerebellar tissue by favoring specific ascending fibers as they cross paths and create synapses with Purkinje cells [5].

Elevation of PGRN level in COVID-19 patients was detected and observed to be more sensitive than CRP level in distinguishing patients with COVID-19 from the healthy people [6].

The aim of this works is to measure levels of progranulin in the serum of adult patients with acute myeloid leukemia [AML] before and after treatment. Next, to correlate their serum levels to prognosis.

PATIENTS AND METHODS

Our prospective observational study was conducted on 40 adult patients with AML recruited from Clinical Hematology and Oncology hospital in Maadi Military Complex before and after chemotherapy treatment during six months. Fifteen adult healthy people with comparable age and sex were subjected as a control group.

The patients received conventional chemo-therapy protocols according to NCCN guidelines for AML treatment. All the participants were asked for their written informed permission prior to their actual involvement in the study. Only patients aged 16 years or more with newly diagnosed AML were included in the study while patients with other type of malignancy or relapsed AML were excluded.

Either routine laboratory investigations including complete blood count and LDH or disease-specific labs as bone marrow aspiration, flowcytometry, Karyotype and FISH were performed. Progranulin level in serum was assessed using ELISA by automated ELISA reader [Dynex DSX ELISA system].

Statistics/data analysis: All data were described by the median statistical description. Statistical comparison was using Mann–Whitney U test. Survival curves were performed by Kaplan–Meier, and RFS and OS were compared with the Log-rank test. A two-sided P value <0.05 was considered statistically significant. All statistical analysis was using SPSS version 22.0 [IBM, NY] and GraphPad Prism 6.0 [San Diego, CA]. Proper statistical analysis that deemed to be necessary was carried out. Data were expressed as number and percentage for qualitative variables and mean + standard deviation [SD] for quantitative one.

RESULTS

Table [1] shows that serum Progranulin levels are significantly higher for AML patients than control group $p<0.001$.

Table [2] shows that there is no significant difference of serum Progranulin levels after chemotherapy treatment compared to its level at diagnosis among AML patients.

Table [3] clarified non-significant difference of serum levels of Progranulin in AML Patients at diagnosis and after chemotherapy regarding sex, present of comorbidity, risk level and outcome of chemotherapy $p>0.05$.

There was no statistically significant correlation between serum levels of Progranulin

at diagnosis or after chemotherapy in AML patients with age, clinical and laboratory findings $p<0.05$ as shown in table [4].

Table [5] shows the sensitivity and specificity obtained to serum levels of Progranulin at diagnosis value for differentiate AML Patients from healthy control. Cut off equal or more than 162.5 ng/ml had 100% sensitivity, specificity, positive predictive value, negative predictive value, and accuracy.

On the other hand, table [6] shows the sensitivity and specificity obtained to serum levels of Progranulin [ng/ml] value for prognosis of AML patients. Cut off equal or less than 347.5 had 63.16% sensitivity and 66.67% specificity, positive predictive value 63.16%, negative predictive value 66.67% and accuracy was 65.0%.

Figure [1] shows the ROC curve of serum levels of Progranulin at diagnosis [ng/ml] to discriminate AML patients from healthy control [AUC]. Serum levels of Progranulin are considered excellent marker for diagnosis AML Patients. Furthermore, figure [2] shows ROC curve of serum levels of Progranulin at diagnosis [ng/ml] for prognosis AML Patients [AUC] 0.644, so serum levels of Progranulin are poor marker for prognosis AML Patients.

Table [1]: Comparison of studied AML Patients and healthy control; regard Serum Levels of Progranulin

Serum Levels of Progranulin at diagnosis [ng/ml]	AML Patients [n=40]	Control group [n=15]	t	p
Mean ± SD		92.73±7.99		
Median	351.5	91	24.36	**0.0001**
Range	215-545	79-110		

Table [2]: Comparison of studied Serum Levels of Progranulin among AML Patients at diagnosis and after chemotherapy treatment

Serum Levels of Progranulin [ng/ml]	AML Patients [n=40]		W	p
	Serum Levels of Progranulin at diagnosis [ng/ml]	Serum Levels of Progranulin post chemotherapy [ng/ml]		
Mean ± SD	346.08±64.46	350.37±102.03		
Median	351.5	355	0.482	0.63
Range	215-545	25-640		

Table [3]: Comparison between Serum Levels of Progranulin in AML Patients at diagnosis and after chemotherapy regarding basic parameters of disease

Variables		Time		Paired t	p-value
		Serum Levels of Progranulin at diagnosis [ng/ml]	Serum Levels of Progranulin after chemotherapy [ng/ml]		
Sex	Females	365±63.14	342.86±76.05	**0.88**	**0.83**
	Males	325.16±60.77	358.68±126.46	**1.09**	**0.28**
	t	2.03	0.48		
	P	0.05	0.63		
Comorbidity	Yes	299±83.5	361.67±40.1	**0.87**	**0.47**
	No	349.89±62.57	349.46±105.7	**0.021**	**0.98**
	t	1.33	0.197		
	P	0.19	0.84		
Risk	High	346.08±62.58	372.75±45.23	**1.12**	**0.28**
	Intermediate	338.18±75.27	310.41±113.9	**0.79**	**0.44**
	Low	358.27±50.63	387.73±112.86	**0.74**	**0.48**
	F	0.313	2.5		
	P	0.73	0.095		
outcome	Alive	334.53±68.32	326.68±127.4	**0.22**	**0.83**
	Died	356.52±60.51	371.81±68.39	**0.74**	**0.47**
	t	1.08	1.41		
	P	0.28	0.16		

Table [4]: Correlation between Serum Levels of Progranulin in AML Patients with age, clinical and laboratory findings

variables	Serum Levels of Progranulin in AML Patients			
	at diagnosis		After chemotherapy	
	r	P	r	p
Age	0.274	0.087	-0.119-	0.464
LDH	-0.185	0.253	0.145	0.372
Blasts [Bone Marrow]	0.213	0.187	-.0184	0.256
Promyelocytes	-0.564	0.322	0.574	0.312
Risk	0.051	0.754	-0.113	0.486
Echo	-0.215	0.182	0.287	0.073

[r]Spearman rank correlation coefficient p>0.05 insignificant

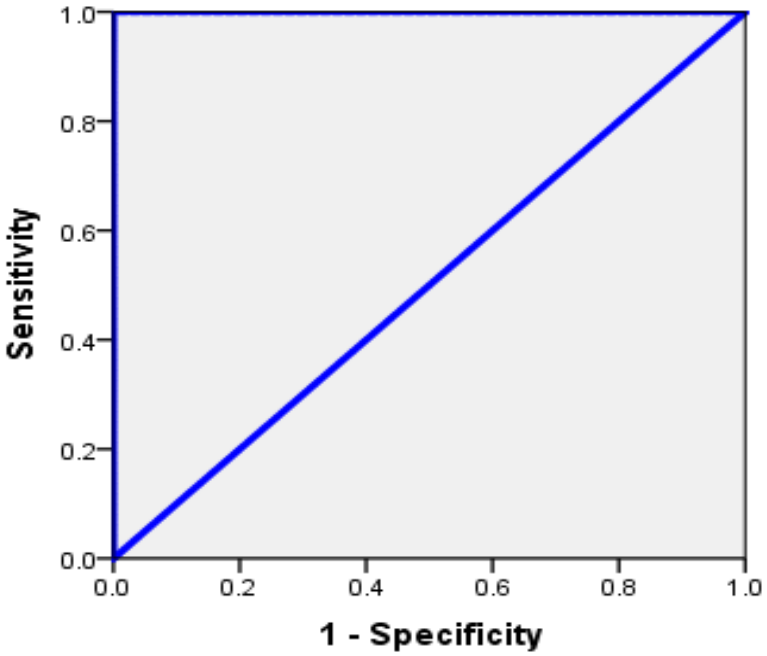


Figure [1]: ROC curve of Serum Levels of Progranulin at diagnosis [ng/ml] to discriminate AML Patients from healthy control [AUC]

Table [5]: Performance of Serum Levels of Progranulin at diagnosis [ng/ml] to discriminate AML Patients from healthy control

Serum Levels of Progranulin at diagnosis [ng/ml]	AML Patients [n=40]	Healthy control [n=15]
Cut off Serum Levels of Progranulin at diagnosis		
≥162.5 ng/ml	40	0
<162.5 ng/ml	0	15
Sensitivity	100.0%	
Specificity	100.0%	
Positive Predictive Value	100.0%	
Negative Predictive Value	100.0%	
Accuracy	100.0%	

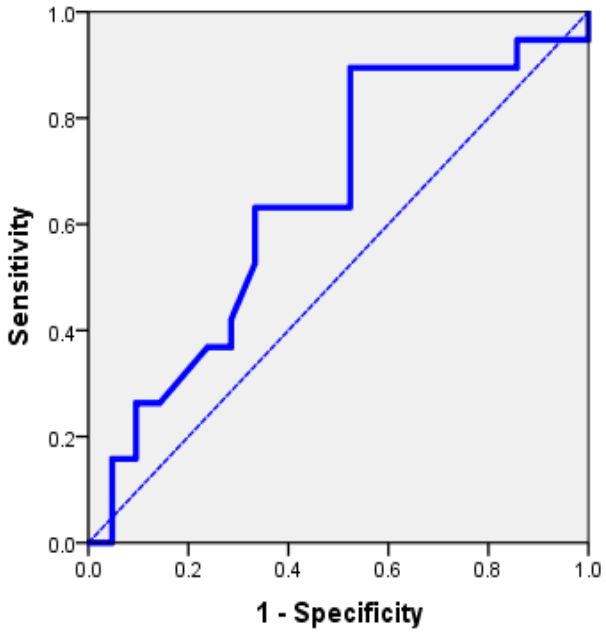


Figure [2]: ROC curve of Serum Levels of Progranulin at diagnosis [ng/ml] for risk level AML Patients. [AUC] 0.644

Table [6]: Performance of Serum Levels of Progranulin at diagnosis [ng/ml] for risk level AML Patients

Serum Levels of Progranulin at diagnosis [ng/ml]	AML Patients	
	Alive [n=19]	Died [n=21]
Cut off Serum Levels of Progranulin at diagnosis		
≤347.5 ng/ml	12	7
>347.5 ng/ml	7	14
Sensitivity	63.16%	
Specificity	66.67%	
Positive Predictive Value	63.16%	
Negative Predictive Value	66.67%	
Accuracy	65.0 %	

DISCUSSION

Progranulin [PGRN], a granule protein precursor, is a recently identified autocrine growth factor. It is widely dispersed and essential for the growth of the embryo, healing of wounds, inflammation, and oncogenesis. For breast cancer patients who have estrogen receptor positive disease, PGRN has been linked to carcinogenesis and anti-estrogen therapy tolerance [7]. The overexpression of PGRN in chronic lymphocytic leukemia had also been studied. Many writers claimed that the PGRN gene's high expression was linked to the occurrence and spread of cancer. The production of PGRN was favorably linked with the tumors' histological grade in endometrial cancer, leiomyosarcoma, and glioma [8].

The aim of the present study is to measure levels of progranulin in the serum of adult patients with acute myeloid leukemia before and after treatment. A comparison of its levels before treatment with a group of control subjects and correlation of their serum levels to prognosis before and after treatment was done.

Serum Progranulin levels were significantly higher for AML patients than control group $p<0.001$ in our study. There was a statistically insignificant difference of serum Progranulin levels after chemotherapy treatment compared to its level at diagnosis among AML patients $p>0.05$.

There was a statistically insignificant difference of serum levels of Progranulin in AML patients at diagnosis and after chemotherapy regarding sex, present of comorbidity, risk level and outcome of chemotherapy $p>0.05$. There was a statistically insignificant correlation between serum

Progranulin levels at diagnosis or after chemotherapy in AML patients with age, clinical and laboratory findings $p<0.05$.

According to sensitivity and specificity obtained to serum Progranulin levels at diagnosis value for differentiate AML patients from healthy control. Cut off equal or more than 162.5 ng/ml had 100% sensitivity, specificity, positive predictive value, negative predictive value, and accuracy. The sensitivity and specificity obtained to serum levels of Progranulin [ng/ml] value for prognosis AML Patients. Cut off equal or less than 347.5 had 63.16% sensitivity and 66.67% specificity, positive predictive value 63.16%, negative predictive value 66.67% and accuracy was 65.0%.

In the **El-Ghammaz *et al.*** [9]'s investigation, there was a significant difference in the serum PGRN level between patients and controls. Age, total leukocyte count, hemoglobin, platelet count, absolute blast count in peripheral blood, lactate dehydrogenase, and percentage of blasts in bone marrow did not significantly correlate with serum PGRN. Moreover, **Qin *et al.*** [8] demonstrated that AML patients with a higher proportion of immature cells in their bone marrow have plasma PGRN concentrations than AML patients with a lower proportion. Results from peripheral blood matched those from bone marrow in many ways. WBC counts in peripheral blood and the level of plasma PGRN expression in AML patients were associated, whereas sex, age, platelet count, and FAB type were not. Also, according to **Yamamoto *et al.*** [10] patients with AML had median serum Progranulin concentrations of 91.3 ng/ml, which was greater than that of the control group. A serum Progranulin cutoff concentration of 68.5 ng/ml differentiated lymphoma patients from healthy controls according to ROC curve analysis.

Conclusion: Our investigation has led us to the conclusion that adult AML patients have elevated PGRN levels, which may be related to the tumor burden in these individuals.

Conflict of Interest and Financial Disclosure: None.

REFERENCES

1. Yamamoto Y, Takemura M, Serrero G, Hayashi J, Yue B, Tsuboi A, Kubo H, Mitsuhashi T, Mannami K, Sato M, Matsunami H, Matuo Y, Saito K. Increased serum GP88 [Progranulin] concentrations in rheumatoid arthritis. Inflammation. 2014 Oct;37[5]:1806-13. doi: 10.1007/s10753-014-9911-4.
2. Ong CH, Bateman A. Progranulin [granulin-epithelin precursor, PC-cell derived growth factor, acrogranin] in proliferation and tumorigenesis. Histol Histopathol. 2003 Oct;18[4]:1275-88. doi: 10.14670/HH-18.1275.
3. Edelman MJ, Feliciano J, Yue B, Bejarano P, Ioffe O, Reisman D, *et al.* GP88 [progranulin]: a novel tissue and circulating biomarker for non-small cell lung carcinoma. Hum Pathol. 2014 Sep;45[9]:1893-9. doi: 10.1016/j.humpath.2014.05.011.
4. Bouchet S, Tang R, Fava F, Legrand O, Bauvois B. The CNGRC-GG-D[KLAKLAK]2 peptide induces a caspase-independent, Ca2+-dependent death in human leukemic myeloid cells by targeting surface aminopeptidase N/CD13. Oncotarget. 2016 Apr 12;7[15]:19445-67. doi: 10.18632/oncotarget.6523.
5. Kashyap SN, Boyle NR, Roberson ED. Preclinical Interventions in Mouse Models of Frontotemporal Dementia Due to Progranulin Mutations. Neurotherapeutics. 2023 Jan;20[1]:140-153. doi: 10.1007/s13311-023-01348-6.
6. Özgeris FB, Koçak ÖF, Kurt N, Parlak E, Yüce N, Keles MS. High Serum Progranulin Levels in COVID-19 Patients: A Pilot Study. Biochemistry [Mosc]. 2022 Mar;87[3]:207-214. doi: 10.1134/S0006297922030026.
7. Rhost S, Hughes É, Harrison H, Rafnsdottir S, Jacobsson H, Gregersson P, *et al.* Sortilin inhibition limits secretion-induced progranulin-dependent breast cancer progression and cancer stem cell expansion. Breast Cancer Res. 2018 Nov 20;20[1]:137. doi: 10.1186/s13058-018-1060-5.
8. Qin J, Huang S, Qian J, Xu C, Li S, Yu S, *et al.* The prognostic relevance and expression of progranulin in adult patients with acute myeloid leukemia. Medicine [Baltimore]. 2020 Jan;99[1]:e18574. doi: 10.1097/MD.0000000000018574.
9. El-Ghammaz AMS, Azzazi MO, Mostafa N, Hegab HM, Mahmoud AA. Prognostic significance of serum progranulin level in de novo adult acute lymphoblastic leukemia patients. Clin Exp Med. 2020 May;20[2]:269-276. doi: 10.1007/s10238-020-00610-x.
10. Yamamoto Y, Goto N, Takemura M, Yamasuge W, Yabe K, Takami T, *et al.* Association between increased serum GP88 [progranulin] concentrations and prognosis in patients with malignant lymphomas. Clin Chim Acta. 2017 Oct;473:139-146. doi: 10.1016/j.cca.2017.07.024.

International Journal of Medical Arts

https://ijma.journals.ekb.eg/
Print ISSN: 2636-4174
Online ISSN: 2682-3780