

## USEFULNESS OF SERUM (1, 3) BETA D GLUCAN IN DIAGNOSIS OF PNEUMOCYSTIS JIROVECI PNEUMONIA IN IMMUNOCOMPROMISED PATIENTS

*Dina Omar Mohamed<sup>1</sup>, Mohamed Sidky Mahmoud<sup>2</sup>, Sally Mohamed Saber<sup>1</sup>, and Yasmeeen Mohammad Mahmood Ali Ibraheem<sup>1</sup>.*

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### ABSTRACT

<sup>1</sup>Department of clinical pathology, and <sup>2</sup>Department of Anesthesia and ICU, Faculty of Medicine Ain Shams University, Cairo, Egypt

**Corresponding author:**  
Dina Omar Mohamed  
Mobile: +201093382427  
e.mail:  
[dina.omar994@gmail.com](mailto:dina.omar994@gmail.com)

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**Background and study aim:** The current study aims to figure out the use of the serological 1, 3 Beta-D-Glucan (BDG) test for early detection of *Pneumocystis jirovecii* Pneumonia (PcP) among immunocompromised patients with acute respiratory distress syndrome (ARDS).

**Patients and methods:** This are a cross-sectional study. It was carried out at Ain Shams University Hospitals on immunocompromised patients presenting with pneumonia. The study included 44 clinically relevant patients, with lower respiratory tract infections, based on their clinical presentation and chest radiological findings. The group included 26 males and 18 females. Their ages ranged from 1 to 74 years.

**Results:** Out of 44 immunocompromised Patients with ARDS caused by Invasive Fungal Infections (IFI) suspected PcP according to clinical, radiological findings and Galactomannan, those patients included patients in ICU, with haematological malignancies, on immunosuppressive drugs and HIV positive Patients. 72.7 % were positive for BDG, while 27.3 % were negative for BDG. Positive predictive value of BDG was 75 % while BDG's negative predictive value 91.7 %. Our results figured out also that there was a statistically significant relation between results of BDG and Galactomannan with Value < 0.001, lymphocytic count with P Value 0.005 and LDH level with P Value 0.017. Sensitivity of the test was 96% while Specificity was 57.9%

**Conclusions:** *Pneumocystis jirovecii* pneumonia represents a huge burden to immunocompromised patients in the intensive care unit (ICU) and those with haematological malignancies, particularly those with lymphoproliferative diseases. Increased rates of ICU admissions for respiratory failure and fatalities are linked to the disease. BDG is a non-invasive diagnostic technique that has a high negative predictive value and can rule out IFI. However, neither do its serum levels accurately reflect the severity of the illness nor are they useful for gauging treatment effectiveness.

**Keywords:** *Pneumocystis Jirovecii* Pneumonia; 1,3 BDG.

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### INTRODUCTION:

Patients with impaired immune systems are more likely to develop *Pneumocystis jirovecii* pneumonia, especially those who

are unwell. High rates of morbidity and mortality are associated with *pneumocystis jirovecii* pneumonia, which is still a dangerous and potentially fatal infection<sup>[1]</sup>.

Antiretroviral therapy has reduced the frequency of PcP in people with HIV, but it has been rising in patients with haematological cancers, autoimmune illnesses, stem-cell or solid-organ transplants, and those receiving systemic chemotherapy<sup>[2]</sup>.

PcP has non-specific radiographic features, although high-resolution computed tomography (HRCT) in certain individuals may show cystic lesions or a "ground-glass" appearance. Immunocompromised patients' clinical and radiographic findings can be highly suggestive of a diagnosis of PcP, but the organism must be identified by colorific staining, fluorescent antibody staining, or polymerase chain reaction (PCR)-based assays of respiratory specimens in order to make a conclusive diagnosis of PcP. <sup>[1]</sup>.

Human specimens are insufficient for successfully isolating *P. jirovecii* in culture. Hence, after microscopic inspection of respiratory specimens using various staining methods, the primary diagnostic criteria for determining PcP is the presence of trophic or cyst forms<sup>[3]</sup>.

In contrast to individuals who are HIV-positive, prior research have found that these techniques' sensitivity is low particularly in non-HIV patients. This issue may make it more difficult to make an early diagnosis and confusing PcP results in critically sick ARDS patients may also be fatal due to the increased morbidity and potential side effects of treatment given an improper indication<sup>[4]</sup>.

Considering the use of Nested PCR in the diagnosis of PcP, it may be a non-invasive and sensitive diagnostic technique that can find extremely minute quantities of *P. jirovecii* in induced sputum samples. The clinical care and PcP outcomes for those patients can therefore be improved. Also, the PCR method may be utilised for a lot of samples at once, and the results can be obtained in a day without any bias that could occur for microscopic examination.<sup>[5]</sup>

A non-invasive useful marker in the early detection of PcP is serum 1,3-Beta-D-Glucan (BDG), a characteristic cell wall component of several pathogenic fungus, including *P. jirovecii*. The FDA has authorised the use of the so-called Fungitell BDG assay (Associates of Cape Cod, East Falmouth, MA) for the detection of invasive fungal infections, such as PcP <sup>[6]</sup>.

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## AIM OF THE STUDY:

The current study aims to figure out the use of the serological 1, 3 Beta-D-Glucan (BDG) test for early detection of *Pneumocystis jirovecii* Pneumonia (PcP) among immunocompromised patients with acute respiratory distress syndrome (ARDS).

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## PATIENTS AND METHODS:

**Study design:** Cross sectional study.

**Study settings:** This study was carried out at Ain Shams University Hospitals on immunocompromised patients presenting with pneumonia during the period from March 2022 till December 2022.

**Sample size:** 44 lower respiratory tract samples (BAL or Sputum) and serum samples (2ml blood will be withdrawn from each Patient)

### Inclusion criteria:

- Immunocompromised patients, fulfilling one or more of the following criteria:
  - Being an ICU patient
  - Organ transplantation patients
  - Patients on immunosuppressive agents
  - HIV- positive patients
- Suspected or confirmed acute respiratory distress syndrome (ARDS)

### Exclusion criteria:

None

**Patient assessment:**

All patients were subjected to:

- Full history taking.
- CBC for assessment of WBC and lymphocytic count
- LDH
- Chest Radiological assessment for confirmation of pneumonia
- Conventional Culture and sensitivity of lower respiratory tract (LRT) sample (Sputum or BAL)
- Serological Galactomannan
- Serological 1,3 Beta-D-Glucan Test by using Sandwich enzyme-linked immune-sorbent assay (ELISA) technique.

**Ethical consideration:**

Permission and official approval to carry out the study was obtained. An informed consent was obtained from all patients prior to their enrolment in the study. They were informed about the aim of our study; methodology and they had agreed to participate in the study and the institutional ethical committee at Ain Shams University, Faculty of Medicine approved the study (FWA000017585).

**Statistical analysis:**

The IBM SPSS software package version 20.0 was used to input data and analyse it (Armonk, NY: IBM Corp). Quantitative data were described in terms of percentage and number. The Shapiro-Wilk test was employed to confirm the distribution's normality. Frequency distributions and relative percentages were used to display qualitative data. The difference between qualitative variables was calculated as shown using the Chi-square test ( $\chi^2$ ), Mann Whitney test (U test), and Fisher exact. For parametric and non-

parametric data, respectively, median and range were used to express quantitative data as mean SD (Standard Deviation). Two-tailed significance tests were used for all statistical comparisons. Level of P-value 0.05 denotes a significant difference, p 0.001 denotes a highly significant difference, and P> 0.05 denotes a non-significant difference.

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**RESULTS:**

*Study participants*

This is a cross sectional Study which was conducted in Clinical pathology department of 44 immunocompromised Patients with ARDS caused by Invasive Fungal Infections (IFI) suspected PCP according to clinical, radiological findings and Galactomannan in Ain shams university hospitals.

As in **Table 1**; 32 out of those 44 Patients (72.7 %) were positive for BDG, while 12 (27.3 %) were negative for BDG.

Patients in this study were classified according to the diagnosis:

16 out of 44 were diagnosed with haematological malignancies; one patient was negative for BDG, while 15 out of 16 were positive for BDG, and it has a significant relation with the study (P value 0.018); 4 out of 44 patients were on immunosuppressive agents; 2 patients were negative for BDG, and two were positive for BDG with no statistically significant difference. (P value 0.297); 23 out of 44 patients were admitted during this period in ICU; 9 patients were negative for BDG, while 14 out of 23 ICU patients were positive for BDG with no statistically significant difference. (P value 0.065); one patient out of 44 patients was HIV positive Patient with ARDS and he was positive for BDG (P value 1).

About values of BDG, Positive predictive value of BDG 75%, False positive results from our study were due to IVIG

administration, Albumin infusion, haemodialysis or combination of Amoxicillin and clavulanic acid, while negative predictive value was 91.7 and false negative results may be due to haemolysed or lipemic samples. Sensitivity of the test was 96% while Specificity was 57.9% **Table 2, Figure 1.**

According to the relation between results of BDG and Galactomannan; Galactomannan cut off is < 0.5 is negative, > 0.5 is positive. 7 patients were positive for both BDG and Galactomannan; 2 patients were negative for both BDG and Galactomannan; 25 patients were positive for BDG only while 10 patients were positive with Galactomannan only. All 44 patients' Galactomannan level was measured

with mean  $0.57 \pm 0.58$  and has a statistically significant relationship with BDG (P value < 0.001); **Table 3; Figure 2.**

According to TLC (Total Leucocytic count), the mean of TLC of all patients  $8.67 \pm 9.96$  with P value 0.016 and it has a statistically significant relation with BDG.

Regarding lymphocytic count, the mean of lymphocytic count of all patients was  $0.76 \pm 0.79$  with P value 0.005 and it has statistically significant relationship with BDG. **Table 4; Figures 3&4.**

Regarding LDH level, the mean of LDH level of all 44 patients was  $544.20 \pm 554.80$  with P value 0.017 and it has a statistically significant relation with BDG results (P value 0.017) **Table 5; Figure 5.**

Table 1: Distribution of the studied cases according to BDG (n = 44)

BDG	No.	%
Negative / equivocal (<95pg/ml)	12	27.3
Positive (>95pg/ml)	32	72.7
Min. – Max.	4.92 – 1000.0	
Mean ± SD.	277.68 ± 240.93	

Table 2: Diagnostic Performance of BDG according to clinical diagnosis

Diagnosis	Total (n = 44)	BDG				P Value	PPV	NPV	Sensitivity	Specificity
		Positive (>95) (n = 32)		Negative / equivocal (<95) (n = 12)						
		TP	FP	TN	FN					
Haematological malignancies	16	13	2	1	0	<sup>FE</sup> p=0.018	86.6	100	100	33.3
Patients on immunosuppressive agents	4	1	1	2	0	<sup>FE</sup> p=0.297	50	100	100	66.7
Medical ICU patient	23	9	5	8	1	0.065	64.3	88.9	90	61.5
HIV patient	1	1	0	0	0	<sup>FE</sup> p=1	100	0	100	0
Total performance of BDG	44	24	8	11	1		75	91.7	96	57.9

n: number, TP: true positive, FP: false positive, PPV: positive predictive value, NPV: negative predictive value)

### *BDG and Pneumocystis Jirovecii Pneumonia*

Table 3: Comparison between the two studied groups according to galactomannan

Galactomannan	Total (n = 44)		BDG				P
			Negative / equivocal (<95) (n = 12)		Positive (>95) (n = 32)		
	No.	%	No.	%	No.	%	
Negative (<0.5)	27	61.4	2	16.7	25	78.1	<sup>FE</sup> p <0.001*
Positive (>0.5)	17	38.6	10	83.3	7	21.9	

Table 4: Comparison between the two studied groups according to WBCs and lymphocytic count

	Total (n = 44)		BDG		P
			Negative / equivocal (<95) (n = 12)		
	WBCs				
Min. – Max.	0.20 – 38.50		1.50 – 29.40		0.016*
Mean ± SD.	8.67 ± 9.96		12.25 ± 8.65		
Lymphocytic count					
Min. – Max.	0.03 – 3.05		0.03 – 2.30		0.005*
Mean ± SD.	0.76 ± 0.79		1.30 ± 0.82		

Table 5: Comparison between the two studied groups according to LDH

LDH	Total (n = 44)		BDG				P
			Negative / equivocal (<95) (n = 12)		Positive (>95) (n = 32)		
	No.	%	No.	%	No.	%	
≤247	3	6.8	3	25.0	0	0.0	<sup>FE</sup> p= 0.017*
>247	41	93.2	9	75.0	32	100.0	
Min. – Max.	122.0 – 3179.0		122.0 – 910.0		280.0 – 3179.0		0.541
Mean ± SD.	544.20 ± 554.80		429.92 ± 250.29		587.06 ± 630.70		

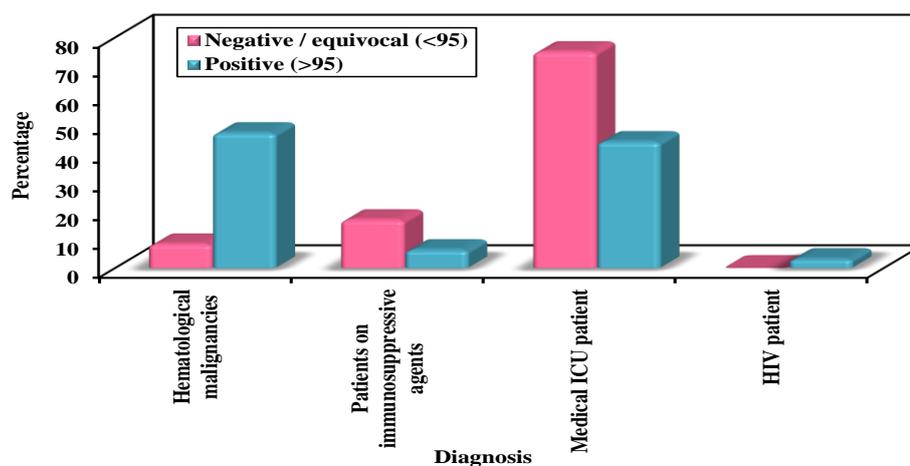


Figure 1: Comparison between the two studied groups according to diagnosis

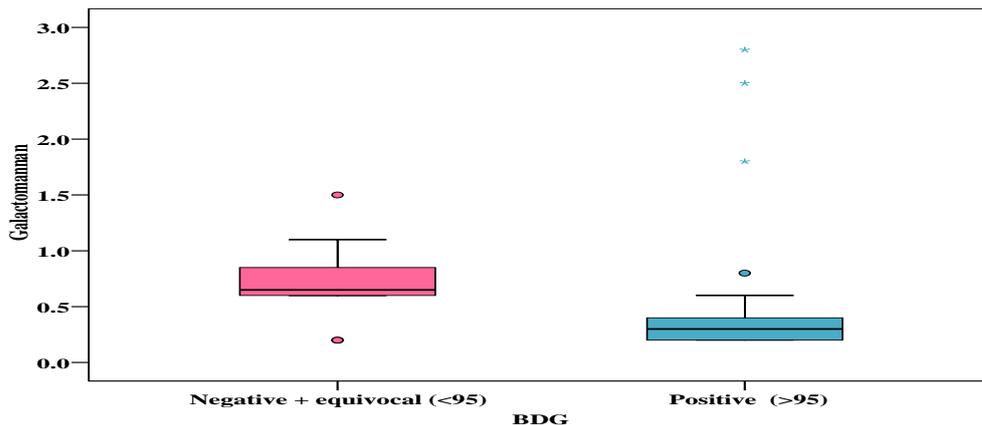


Figure 2: Comparison between the two studied groups according to galactomannan

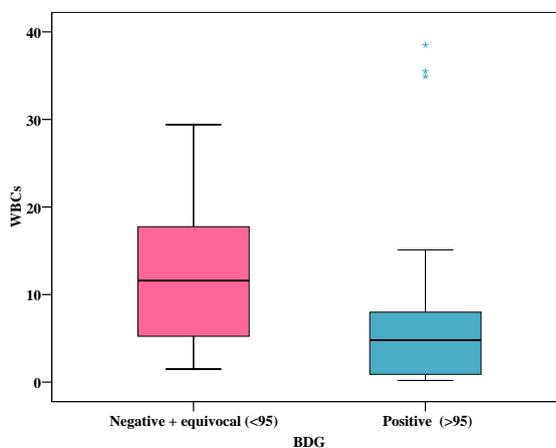


Figure 3: Comparison between the two studied groups according to WBCs

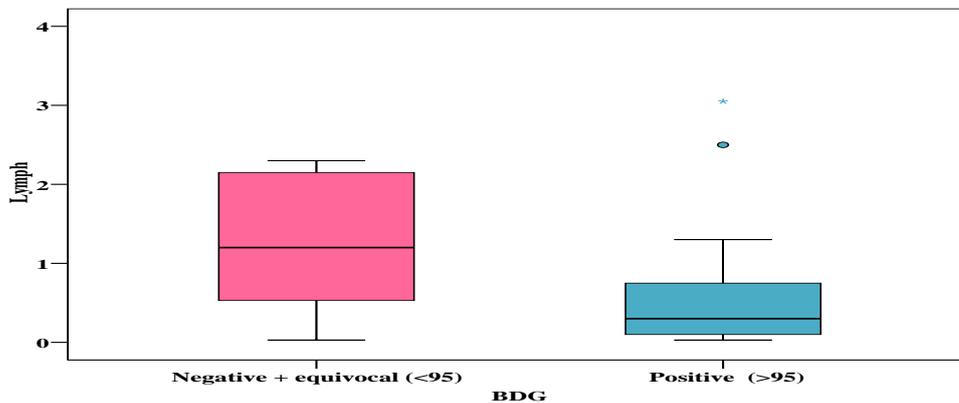


Figure 4: Comparison between the two studied groups according to lymphocytic count

## BDG and *Pneumocystis Jirovecii* Pneumonia

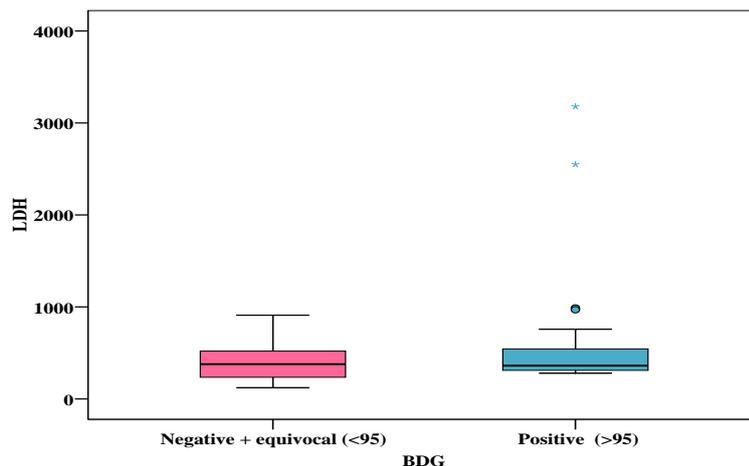


Figure 5: Comparison between the two studied groups according to LDH

### DISCUSSION:

The most common causes of fungal disease, *Aspergillus* spp. and *Candida* spp., as well as many other important fungi for medicine, such as *P. jirovecii*, have a significant amount of B-D-Glucan in their cell walls. As a result, it is regarded as a "pan-fungal" marker [7].

Several studies have assessed the test performance for detecting serum B-D-glucan to diagnose PcP. Some researchers looked at this marker in patients with HIV infection, while others used mixed populations that comprised patients with HIV infection and patients who were receiving various types of immunosuppression, while still others looked at this marker in just patients who were HIV-negative [8].

In this cross-sectional study, B-D-Glucan test was used to evaluate the usefulness of it for the diagnosis of PcP.

An increase in BDG concentration over 95 pg/ml is regarded as positive in accordance with the manufacturer's interpretation standards. Indeterminate results are still obtained at concentrations between 70 and 94 pg/ml. Based on a sizable prospective analysis of patients receiving initial induction chemotherapy for acute myelogenous leukaemia or myelodysplastic syndrome, Odabasi et al. [9] established a cut

off value of 60 pg/ml for the identification of invasive fungal infections. Based on a retrospective investigation conducted on HIV-positive patients and patients with haematological malignancies, Desmet et al. [10] established an 80 pg/ml cut off value for the identification of invasive fungal infections.

In PcP, BDG's positive predictive value was just 75%. The impact of a number of confounding factors that are still unknown may help to explain this. Moreover, BDG is increased in most other invasive fungal infections in addition to PcP. Because of this, BDG levels by themselves cannot establish the presence of PcP, and they should not be interpreted without taking into account the clinical outcome.

However, a BDG level of 95 pg/mL or lower virtually completely excludes PcP, and this could be very helpful for patients who cannot have bronchoscopy procedures or for patients in whom there is little clinical suspicion of PcP, this cross sectional study revealed a negative predictive value of 91.7% for BDG.

There is little information available, and the findings are not definitive, regarding the relationship between BDG levels and patient outcomes [11].

In chest X-rays and CT scans, bilateral

interstitial pulmonary infiltration was the most frequent finding in BDG. Patients that tested positive for PcP, Zahar et al.<sup>[12]</sup> and Hafez et al.<sup>[13]</sup> both reported findings that were comparable<sup>[13]</sup>

The severity rate in HIV-infected patients in case of co-infection with PcP ranges from 17 to 30%, although in non-HIV-infected immunocompromised patients are higher ranging from 28 to 53%<sup>[7]</sup>.

The majority of the patients in this study were ventilated or post-arrest, and the current study findings revealed that the serum level of BDG does not accurately reflect the severity of PcP in patients with AIDS. Despite the fact that Shimizu et al.<sup>[14]</sup> claimed that b-d-glucan is a poor predictive predictor for PcP in patients with connective tissue illnesses, there was no discernible difference in b-d-glucan levels between survivors and non survivors in our investigation.

For patients with high and low BDG levels, there was no significant difference in the severity of PcP, according to our data analysis. In agreement with Nakamura et al.<sup>[15]</sup> and Watanabe et al.<sup>[16]</sup>, they were unable to discover a discernible difference in BDG levels between survivors and non-survivors at this point. However, Damiani et al.<sup>[17]</sup> claimed that they found a link between high BDG levels and a bad prognosis.

Although the maximal BDG level throughout hospitalisation and the absolute BDG level upon diagnosis don't seem to be related to prognosis, this may be different for BDG kinetics. The correlation between a positive outcome and declining BDG levels has been demonstrated in individual cases<sup>[18]</sup>. However, more research is obviously required to support these observations in larger series.

The global incidence of PcP in haematology patients post allogeneic and autologous stem cell transplantation between 1995 and 2005 was 0.63% and 0.28%,

respectively<sup>[19]</sup>.

In the current work, 46.9% of BDG positive patients and suspected PcP, had hematological malignancies. Similarly, Pagano et al.<sup>[20]</sup> found that 58% of their studied PcP positive patients had hematological malignancies. A similar finding was also reported by Hafez et al.<sup>[13]</sup> and Oren et al.<sup>[21]</sup>.

According to the relation between results of BDG and Galactomannan; Galactomannan cut off is  $< 0.5$  is negative,  $> 0.5$  is positive. 7 patients were positive for both BDG and Galactomannan; 2 patients were negative for both BDG and Galactomannan; 25 patients were positive for BDG only while 10 patients were positive with Galactomannan only. All 44 patients' Galactomannan level was measured with mean  $0.57 \pm 0.58$  and has a high significance with BDG (P value  $< 0.001$ ).

These results might be due to broad spectrum of BDG to diagnose invasive fungal infections (IFI) while galactomannan detects Aspergillus infection. And the reason for negativity of BDG in some positive galactomannan patients may be that BDG has lower sensitivity in patients with localized Aspergillus infection<sup>[22]</sup>.

BDG testing in conjunction with LDH levels allows for a completely non-invasive sampling procedure and has been successfully tested for the diagnosis of PcP. Specificity was 84% when utilising the best criteria, which were 400 pg/ml for BDG and 350 u/l for LDH<sup>[11]</sup>.

According to LDH level in relation with BDG in our cross-sectional study, LDH cut off level was 247 IU/L

LDH level of all 44 patients were measured with a mean =  $544.20 \pm 554.80$  and LDH has a statistically significant relation with BDG results.

Out of 44 patients, 3 patients had low level of LDH, and all 3 patients were BDG

negative.

The findings of the present study supported the presumption that serum BDG levels are a valid predictor of PcP, and that a potential alternative method for diagnosing PcP might be achieved by combining serum BDG and LDH levels with clinical diagnosis characteristics.

These results agree with Desmet et al. [10]; Kaplan et al. [23] and Esteves et al. [24] studies.

In the present study, there was a significant difference between BDG Positive patients suspected PcP and BDG negative patients regarding the TLC and the lymphocyte count. An inverse correlation existed between the positivity of BDG suspected PcP and the TLC as well as the presence of positive BDG suspected PcP and the lymphocyte count.

Our findings are consistent with those of (Pagano et al.) [20], who discovered that 60% of the patients they looked at had lymphocyte counts under  $1 \times 10^3/\text{mm}^3$ . The scientists also noted a strong correlation between lymphopenia and PcP mortality. The same results were also reported by (Hafez et al. [13]; Saito et al. [25] and Weng et al. [26]).

**In conclusion:** Immunocompromised patients with haematological malignancies, particularly those with lymphoproliferative diseases and ICU patients, are at high risk of developing pneumocystis jirovecii pneumonia. Increased rates of ICU admissions for respiratory failure and fatalities are linked to the condition. BDG may be regarded as a non-invasive diagnostic technique with high negative predictive value that can roll out IFI. The severity of the condition is not reflected in its blood levels, and it is not a good indicator of how well a treatment is working.

**Author contribution:** In our study all listed authors have made substantial contributions to all of the following three

parts of the manuscript:

- research design, or acquisition, analysis or interpretation of data.
- drafting the paper or revising it critically.
- approving the submitted version.

We also declare that no-one who qualifies for authorship has been excluded from the list of authors.

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#### **Conflict of interest**

None

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## فائدة اختبار بيتا دي جلوكان في تشخيص المكيسات الرئوية الجيروفيسية في مرضى نقص المناعة

دينا عمر محمد حسب رزق<sup>١</sup> و محمد صدقي محمود<sup>٢</sup> و سالي محمد صابر<sup>١</sup> و ياسمين محمد محمود علي<sup>٢</sup>

<sup>١</sup> قسم الباثولوجيا الإكلينيكية، كلية الطب – جامعة عين شمس

<sup>٢</sup> قسم التخدير و الرعاية المركزة ، كلية الطب – جامعة عين شمس

يعاني مرضى نقص المناعة وخاصة الحالات الحرجة من تزايد خطر الإصابة بالالتهاب الرئوي بالمتكيسة الرئوية الجيروفيسية (PCP). ويعد الالتهاب الرئوي بالمتكيسة الرئوية الجيروفيسية عدوى خطيرة ومهددة للحياة حيث يرتبط بارتفاع معدلات المراضة والوفيات.

وبما أن الالتهاب الرئوي الذي تسببه المتكيسة الرئوية الجيروفيسية PCP يسبب مراضة خطيرة، فإن التشخيص المبكر يبنى بنتائج أفضل لهؤلاء المرضى.

تم استخدام بيتا د- جلوكان ١،٣ في هذه الدراسة الرصدية للكشف المبكر عن التهاب الرئة بالمتكيسة الرئوية الجيروفيسية وربما التمييز في النتائج التشخيصية غير المذكورة بوضوح في المرضى الذين يعانون من نقص المناعة بشكل خطير ويصابون بمتلازمة ضيق النفس الحاد.

وقد تم إجراء هذه الدراسة بمعمل الميكروبيولوجي الرئيسي بقسم الباثولوجيا الإكلينيكية بمستشفيات جامعة عين شمس بالتنسيق مع وحدة الرعاية المركزة .

وقد استغرقت هذه الدراسة عام اعتباراً من مارس ٢٠٢٢ حتى مارس 2023

وقد تم إجراء هذه الدراسة على مرضى الحالات الحرجة الذين يُشتبه في إصابتهم بعدوى الجهاز التنفسي السفلي والذين قد يكونون مرضى بوحدة العناية المركزة، والمرضى الخاضعين لإجراءات زرع الأعضاء، والمرضى الخاضعين للعلاج بالمواد المثبطة للمناعة، والمرضى المصابين بفيروس نقص المناعة البشرية وفقاً لإجراءات علم الأحياء الدقيقة القياسية التي يتم إجراؤها في معمل الميكروبيولوجي الرئيسي بقسم الباثولوجيا الإكلينيكية بمستشفيات جامعة عين شمس..

وقد تم أخذ ٤٤ عينة من المسالك التنفسية السفلية (BAL أو البصاق) وعينات الدم من المرضى الخاضعين للدراسة

وقد خضعت جميع العينات للتعرف و التقييم من خلال مزرعة البصاق التقليدية واختبار بيتا دي جلوكان المصلي ١، ٣ باستخدام تقنية ELISA Sandwich و اختبار Galactomannan و الفحص بالأشعة السينية أو المقطعية للجهاز التنفسي.

و تم إجراء الدراسة وفقاً لشروط اللجنة الأخلاقية والعلمية بجامعة عين شمس.

وقد أوضحت الرسالة ان عدد ١٢ من أصل ٤٤ مريض نتائجهم كانت سلبية لإختبار بيتا دي جلوكان ٣و١ المصلي حيث أن النسبة الأقل من 95 pg/ml تعد سلبية بينما كانت نتائج ال ٣٢ مريض الآخرين إيجابية للإختبار و كانت نتائجهم أعلى من 95 pg/ml .

و لم يوجد إختلاف ذو دلالة إحصائية عند تقسيم المرضى إلى ذكور و إناث أو تقسيمهم على حسب السن .

وقد أوضحت الرسالة وجود علاقة بين اختبار بيتا دي جلوكان ٣و١ المصلي و اختبار Galactomannan و تواجده دلالة إحصائية عالية بين خلايا الدم البيضاء الليمفاوية .

وقد استنتجنا من الرسالة ان الالتهاب الرئوي بالمتكيسة الرئوية الجيروفيسية PCP عند المرضى اللذين يعانون من الاورام الدموية الخبيثة أو مرضى نقص المناعة يرتبط بزيادة احتمالية احتياج المريض للعناية المركزة نتيجة الفشل التنفسي كما ارتبط بزيادة معدل الوفيات.

و يعد اختبار بيتا دي جلوكان ٣و١ المصلي إجراء تشخيصي غير تداخلي على الرغم ان نسبة وجوده لا تعكس خطورة المرض و غير مناسبة لمتابعة الاستجابة للعلاج بينما كانت النتائج السلبية كانت لها دلالة واضحة بعدم الإصابة بالالتهاب الرئوي الناتج عن المتكيسة الرئوية الجيروفيسية.