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Automated Blood Cell Counting in Candidaemia: A Comparative Study of Sysmex-X Series 500 and KX-21 Counters

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ABSTRACT

Background: Hidden fungal infections may lead to errors in blood cell counts and inappropriate treatment selection with serious consequences in many patients. This study aimed to evaluate the results of two automated blood cell counters Sysmex-X 500 and KX-21 in samples containing *Candida albicans* and *Candida glabrata.*

Materials & Methods: In this study, 144 blood samples of O- blood type were examined in the presence and absence of *C. glabrata* and *C. albicans* fungi at different concentrations by two automated blood cell counters Sysmex-X 500 and KX-21 in Lorestan University of Medical Sciences in 2017. Fungal samples were prepared at a concentration of 0.5 McFarland, equally added to the blood samples, and read by Sysmex-X 500 and KX-21.

Findings: The average number of erythrocytes, leukocytes, and platelets read by Sysmex-X 500 and KX-21 devices increased in the presence of both fungal samples compared to the primary samples. In addition, the number of lymphocytes, neutrophils, and monocytes read by Sysmex-X 500 and KX-21 devices in the presence of fungal samples was significantly higher compared to the primary samples ($p< .05$). The increase in mean blood cell counts in the presence of both fungal samples was significantly higher in X 500 than in KX-21 ($p< .05$).

Conclusion: This study results showed that among these two devices, the Sysmex-X Series 500 device showed less variation compared to the actual values of blood cells. The use of this device seems to reduce measurement error in blood cell counting.

Keywords: *Candida glabrata*, *Candida albicans*, Leukocytes, Erythrocytes, Platelets .

CITATION LINKS

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Introduction

Invasive fungal infections are associated with significant mortality in hospitalized patients [1-4]. *Candida* species are the most common causes of invasive fungal infections, accounting for about 15% of nosocomial infections and more than 72% of fungal infections in hospitals [2, 5, 6]. In addition, *Candida* species are the third or fourth most common infections isolated from central venous catheter in patients [2, 5, 7]. The gold standard for diagnosis of candidaemia is blood culture. In the microscopic view, yeasts are visible with bud and pseudohyphae, phagocytes in white blood cells are also visible in the microscopic view [8, 9]. *Candida* concentration is usually low in patients with candidaemia (about 10 CFU/mL). Nevertheless, the diagnosis of candidaemia using peripheral blood smear requires a minimum yeast concentration of 10^5 CFU/mL, which requires blood culture [10, 11]. The period required to culture different *Candida* species varies based on the blood sample and could take up to 48 hours [10-12]. What is important in the treatment of fungal diseases is the time required to obtain a positive culture result, which is necessary for determining an appropriate therapeutic approach in the clinic [1, 10, 11].

A high frequency of laboratory errors is annually reported in a large number of laboratory processes. In one study, the error rate was determined to be 0.05-0.61%, and the error distribution in the test stages was reported to be at a maximum rate of 32-75% in the pre-test stage and at a lower rate of 13-32% during the test. Some studies have shown that high levels of candidaemia in the blood lead to laboratory interference in the counting of blood variables such as leukocytes and platelets, which leads to laboratory errors and the selection of inappropriate therapeutic approaches [10, 11]. An automated cell counter is a type of flow cytometry that plays a very important role in the blood section of modern laboratories [13]. Such equipment could analyze a large number of cells with a diameter of 1-30 µm in a short time with high accuracy and repeatability and at a lower cost than the manual method with a microscope [10, 11]. In medical diagnostic laboratories, microscopic examination is mainly performed only when the sample is marked by the device as "requiring further examination" or when the physician requests to examine the extent of peripheral blood [10, 14]. Some studies have shown that high concentrations of *Candida* in the blood lead to mistakes in leukocyte counts read by automated cell counters [1, 10, 15, 16]. The development of candidiasis with fungal factors may lead to incorrect platelet counts in the CELL-DYN 4000 device and incorrect blood analysis of thrombotic patients [15, 16]. These false findings could be very worrisome in patients with simultaneous fungal infections and thrombocytopenia or leukocyte problems as mistakes in platelet and leukocyte counts have serious consequences in these patients and may lead to the selection of wrong treatment approaches [10, 11, 16]. Identifying a suitable method to reduce these laboratory errors could be very useful.

Objectives: This study aimed to evaluate the effect of candidaemia on hematological indices of complete blood count (CBC) test and to compare these indices in automated cell counters Sysmex-X Series 500 and KX21.

Materials and Methods

In this study, blood samples infected with *Candida albicans* and *Candida* were analyzed using Sysmex-X S500i and KX-21 automated blood cell counters in Lorestan University of Medical Sciences in 2017. The choice of these devices was due to limited access and non-duplication in relevant studies, while the selection of O- blood group and specific

yeast species was done in order to minimize confounding factors, address prevalent infections, and examine the impact of device error.

Study population, sampling method, and sample size: Complete blood samples of O- blood type collected from the blood transfusion organization in Khorramabad in 2017 formed the study population. O^- blood type was used to control for antigen interactions between red blood cells and yeasts, considering that in a separate experiment, the effect of yeasts with different concentrations on this blood group was investigated, and no effect was detected. In this study, the sample size was estimated to be 144 samples taking into account the three study groups (*C. glabrata, C. albicans,* and control), two automated blood cell counters Sysmex-X S500i and KX-21, and four replications.

Implementation method: After preparing complete and fresh blood samples of O^- blood type from the blood transfusion organization in Khorramabad and providing standard fungal samples of *C. glabrata* (PTCC: 5297) and *C. albicans* (PTCC: 5072), the experiment was conducted as follows: In the first step, normal saline and standard blood samples (LOT: ST0319N) were tested on X S500i and KX-21 devices to check the correctness and measure the accuracy of these devices. Based on the quality control protocol of laboratory devices, the peripheral blood cell counter should count all parameters in normal saline and standard blood samples based on preset values. To measure the accuracy of the devices, the reading of control samples was repeated three times. If the results did not match, the device was re-calibrated.

In the second stage, the primary blood sample (control group) was read by X S500i and KX-21 devices, and the results were recorded. In the third stage, the *C. albicans* (Group A) and *C. glabrata* (Group B) samples were prepared at a primary concentration of 0.5 McFarland, while the readings and results of both X S500i and KX-21 devices were recorded. In the fourth stage, five concentrations of 0.5, 0.25, 0.125, 0.0625, and 0.0312 cell/mL were prepared from the primary blood sample (Group C) relative to the primary concentration by inoculating normal saline to the primary blood sample. Then X S500i and KX-21 devices read the blood indices in the samples, and the results were recorded. In the fifth stage, *C. albicans* (Group A) and *C. glabrata* (Group B) with the primary concentration were added to the primary blood sample (Group C), and five diluted samples were prepared at concentrations of 0.5, 0.25, 0.125, 0.0625, and 0.0312 cell/mL relative to the primary concentration. Then X Series 500 and KX-21 devices read the blood indices in the samples, and the results were recorded. Dilution of the mentioned groups was done by serial methods, and the dilution rate was similar in different groups with respect to the number of groups. In the sixth step, the erythrocyte sedimentation rate (ESR) was measured in the samples of Groups A, B, and C. The selection of the specific number of dilutions was based on previous studies [10] conducted on blood samples of infected patients in laboratory environments. Taking into consideration the objectives of this study, the researchers decided to choose a range of dilutions that would allow them to capture the maximum and minimum error rates.

By preparing a variety of dilutions, this study aimed to assess the impact of different concentrations on the accuracy and reliability of experimental measurements.

Statistical analysis: After collecting data, they were coded and analyzed by SPSS software Version 16. Descriptive statistics including frequency distribution, central

indices, dispersion, and percentage were used to describe the characteristics of the samples. In addition, in order to compare the results of two Sysmex models of X Series 500i and KX-21 in different groups with different concentrations, inferential statistics including Kolmogorov–Smirnov test, Levene's test, Chi-square, Fisher's exact test, independent T test, and Mann-Whitney test were used. The significance level in this study was 0.05.

Findings

In this study, the variables were measured in the primary blood samples and blood samples mixed with *C. albicans* and *C. glabrata* by two Sysmex models of X Series 500 and KX-21. The results showed that there was no significant difference in the reading of blood indices in the primary blood samples between the two devices (p> .05). There was also no significant difference in the reading of blood indices in the diluted primary samples between the two devices (p> .05). The fungal samples of *C. albicans* and *C. glabrata* at initial concentration (0.5 McFarland) were read by X S500i and KX-21 devices. These two devices tested the fungal samples for WBC (white blood cell) and platelet parameters, and the other values were zero. The mean WBC count in KX-21 and X S500i devices was 5638.33 ± 297.106 and 5762.66 ± 413.62 per µL, respectively. The mean platelet count in KX-21 and X S500i devices was 6685.66 ± 3685.32 and 6859.66 ± 3605.12 per µL, respectively. Statistically, there was no significant difference in the mean WBC and platelet counts read by KX-21 and X S500i devices between the two samples prepared with initial concentrations 0.5(McFarland) of *C. albicans* and *C. glabrata* (p> .05).

The results of this study showed that the mean RBC (red blood cell) counts read by KX-21 in blood samples containing *C. albicans* and by both KX-21 and X S500i in blood samples containing *C. glabrata* increased significantly compared to the primary samples (p< .05) (Fig. 1, parts A and B). The mean WBC counts read by X S500i in blood samples containing *C. albicans* and by KX-21 in blood samples containing *C. albicans* and *C. glabrata* increased significantly (p= .01) (Fig. 1, parts C and D). The increase in WBC count in blood samples containing *C. albicans* in the KX-21 device (mean difference: 460, 95% CI: 36.58 to 883.4) was not significantly different from that in the X S500i (mean difference: 455, 95% CI: 31.58 to 878.4) (p=.154).

The mean platelet counts read by KX-21 and X S500i devices in blood samples containing *C. albicans* increased significantly compared to the primary samples (p< .05). However, this increase in platelet count was significantly greater in KX-21 (mean difference: 20000, 95% CI: 5284 to 34716) than in X S500i (mean difference: 14000, 95% CI: -715/6 to 28716) (p= .022) (Fig. 1, part E). In addition, the mean platelet counts read by KX-21 and X S500i devices in blood samples containing *C. glabrata* significantly increased compared to the primary samples (p<.01). This increase in platelet count was significantly greater in the KX-21 device (mean difference: 16000, 95% CI: 3506 to 28494) than in the X S500i (mean difference: 12500, 95% CI: 906.5 to 24994) (p=.034) (Fig. 1, part F). Increased platelet counts in blood samples containing *C. glabrata* were detected by the KX-21 device at a concentration of 0.5 (p< .05).

The mean hemoglobin (Hb), hematocrit (HCT), corpuscular volume (MCV), and corpuscular hemoglobin (MCH) measured by KX-21 and X S500i devices were lower in *C. albicans* and *C. glabrata* containing samples than in the primary samples. However, this difference was not statistically significant in any of the devices and samples (p> .05).

In samples diluted at 0.5, 0.25, 0.125,

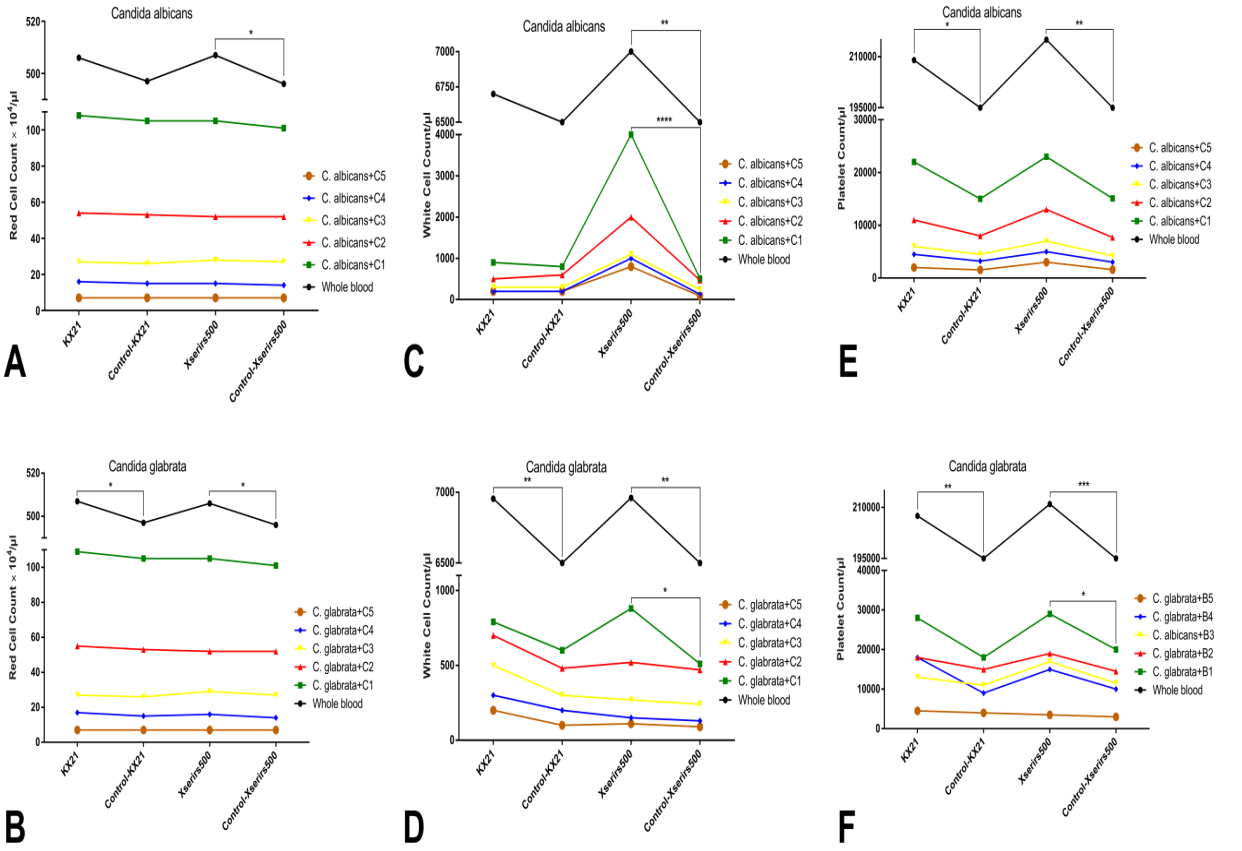

Figure 1) Chart of blood indices measured by KX-21 and X S500i devices in blood samples containing *C. albicans* and *C. glabrata*. A) RBC levels in samples containing *C. albicans*, B) RBC levels in blood samples containing *C. glabrata*, C) WBC levels in samples containing *C. albicans*, D) WBC levels in samples containing *C. glabrata*, E) platelet levels in samples containing *C. albicans,* and F) platelet levels in samples containing *C. glabrata*

0.0625, and 0.0312 cell/mL compared to their primary concentration, the results showed that only the mean WBC count read by the KX-21 device in fungal blood samples (containing *C. albicans* and *C. glabrata*) diluted to a concentration of 0.5 cell/mL relative to the primary concentration was significantly higher than in the control sample ($p< .05$) (Fig. 1, parts C and D). The results of this study showed that the KX-21 device falsely showed an increase in WBC count in fungal blood samples. In addition, platelet counts in diluted samples increased in the presence of *C. albicans* and *C. glabrata* in both devices. Nevertheless, these changes were not statistically significant ($p> .05$).

In this study, WBC reading in the samples based on the cell type showed an increase in all cell types. Lymphocyte and neutrophil counts read by both KX-21 and X S500i devices were significantly higher in blood samples containing *C. albicans* than in the primary samples ($p< .05$) (Fig. 2, part A). In addition, in samples containing *C. glabrata*, only KX-21 showed a significant increase in lymphocyte and neutrophil levels compared to the primary samples ($p< .05$) (Fig. 2, part B). Moreover, monocyte, eosinophil, and basophil levels read by X S500i in samples with *C. albicans* and *C. glabrata* were not significantly different from those in the primary samples ($p> .05$).

Discussion

Annually, invasive fungal infections affect a large number of people for various reasons

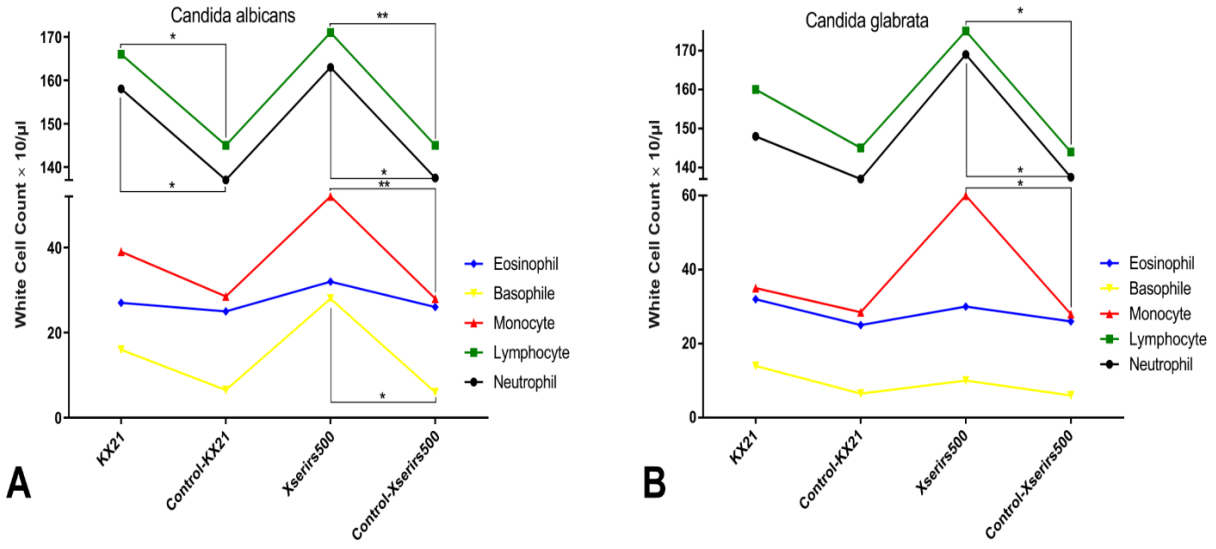

Figure 2) WBC count based on cell type measured by KX-21 and X S500i devices in blood samples containing *C. albicans* and *C. glabrata*. A) The levels of WBCs in samples containing *C. albicans* and B) the levels of WBCs in samples containing *C. glabrata*

[1, 2, 17, 18]. These infections are one of the most common nosocomial infections associated with high mortality in hospitalized patients due to their difficult diagnosis and treatment [1, 2, 5-7, 19]. If patients develop candidaemia, some of their clinical and laboratory symptoms may change [20, 21]. It is noteworthy that there is no reliable method to differentiate benign candidaemia from invasive candidiasis in visceral organs [22]. The concentration of *Candida* in the blood of patients with candidaemia is usually low, and the diagnosis of candidaemia using a peripheral blood smear requires a minimum yeast concentration of 10^5 CFU/mL [23]. Therefore, in the microscopic examination, the presence of yeast (*Candida* species) in the peripheral bloodstream strongly suggests the possibility of a fungal infection [5-7, 24]. In cases where the concentration of *Candida* in the blood is high, leukocyte counting could be performed by automated cell counters [1, 10, 11, 15, 16]. If these fungal infections are not recognized, these changes could be misleading and sometimes lead to mistakes in the treatment process [10, 11]. Studies have shown changes in blood variables in people with *Candida* infection [1, 5, 6, 25, 26]. However, automated blood cell counters generally improve the quality of blood cell analysis compared to conventional microscopy techniques, but a number of potential interfering factors have been identified for such devices, including falsely high platelet counts after bacteremia and microspherocytosis. These false findings could be very worrisome in patients with two simultaneous conditions, patients with fungal and bacterial infections and thrombocytopenia or leukocyte problems, those undergoing chemotherapy, and pregnant women, and mistakes in platelet and leukocyte counts may have serious consequences in these patients and may lead to the selection of inappropriate treatment methods [23, 27-30]. Therefore, identifying appropriate strategies to reduce these laboratory errors could be very valuable. Using a right device with the least possible error could be very important in the patient's

treatment process. The two automated cell counters Sysmex-X S500i and KX-21 are among the most commonly used devices to measure the number of blood cells and their variables, and this study was conducted to identify the device with the least error. The results of this study showed no significant difference in the reading of blood indices in the primary blood samples and the diluted samples between the two devices. However, the levels of blood indices increased in the presence of *C. albicans* and *C. glabrata*. *Candida* species are polymorphic yeasts with a diameter of 2-12 µm, spherical shape, and thin wall, which duplicate through budding [31]. *C. albicans* is a dimorphic species that could grow into hyphae or yeast, which is limited to species that could form true hyphae, pseudomycelium, and chlamydoconidia. *C. albicans* is the most common and pathogenic species among *Candida* species. *C. glabrata* is a nondimorphic species that grows only in the form of yeast and could not form hyphae. *C. glabrat*a is the third most common cause of candidiasis among human infections, which has inherent resistance to azole compounds. *Candida* species also have species-dependent changes. Phenotypic changes or transformation of yeast to hyphae is one of the most important factors in *Candida* species. In the pathogenesis of *Candida*, yeasts contribute to the spread of infection, and hyphae contribute to host tissue damage [32]. Since *Candida* species are similar to white blood cells, red blood cells, and blood platelets in terms of size and morphology, they are misread by cell counters, leading to false reports of increased blood cells.

The mean RBC and WBC counts read by both KX-21 and X S500i devices increased in blood samples containing *C. albicans* and *C. glabrata* in comparison with the primary samples. This increase in RBC and WBC counts in the KX-21 device was significant in both samples containing *C. albicans* and *C. glabrata*. However, the increase in RBC and WBC counts in X S500i was only significant in the samples containing *C. glabrata*.

The mean platelet levels were significantly higher in the samples containing *C. albicans* and *C. glabrata* than in the primary samples. This increase in platelet levels in blood samples containing *C. glabrata* was significantly greater in the KX-21 device than in the X S500i. The results of this study showed a false increase in WBC levels in blood samples containing fungal specimens in the KX-21 device. In addition, platelet counts in diluted samples increased in the presence of *C. albicans* and *C. glabrata* in both devices. However, these changes were not statistically significant.

Lymphocyte and neutrophil levels read by KX-21 and X S500i were significantly higher in blood samples containing *C. albicans* than in the primary sample. In addition, in samples containing *C. glabrata*, only the KX-21 showed a significant increase in lymphocyte and neutrophil levels compared to the primary sample. Moreover, monocyte, eosinophil, and basophil levels read by X S500i in samples with *C. albicans* and *C. glabrata* were not significantly different from those in the primary samples. It is noteworthy that the cell count in KX-21 is partially differential as it does not show the number of monocytes, eosinophils, and basophils separately. But X S500i is fully differential. This feature is one of the most important features of the X S500i vs. KX-21. Various studies have reported errors in measuring blood cells in cases of fungal infections. Bacteria and yeasts may falsely increase WBC and platelet counts due to their presence in the body. Some bacteria may be observed in peripheral blood smear and confirmed by positive blood culture. *Candida* species may also be similar in size to platelets and some white blood cells such as lymphocytes and neutrophils and may

be observed in peripheral blood smears. They have recently been shown in several studies to increase WBC and platelet counts in thrombocytopenic patients, patients with immunodeficiency and reduced immunity, and patients with *Candida* infection [1, 15, 16, 31]. In a case study by Cozzarelli et al. (2017) on a patient with T-cell lymphoma and then cytopenia and apraxia after chemotherapy, the absence of infection and the discontinuation of antibiotic therapy on the 17th day caused WBC and platelet counts read by SYSMEX-XN9000 to be falsely reported above the normal range. In the microscopic examination of the patient's blood culture, the mentioned researchers reported the presence of a large number of extracellular pseudohyphae, germinated yeasts, and *C. parapsilosis* in the patient's blood [32]. Furthermore, in a study by Hirai et al. (2015), a similar problem was reported in a patient with diabetes and hypopituitarism, who was repeatedly admitted with the diagnosis of adrenal insufficiency and pneumonia [33]. A study by Arnold and colleagues (1999) reported that *C. glabrata* fungal infection could lead to incorrect platelet counts on the CELL-DYN 4000 device and incorrect blood analysis in thrombotic patients [15]. Latif et al. (2003) confirmed these results. In their study, they stated that despite the presence of thrombocytopenia in the examined samples, misdiagnosis of the device led to false reports of increased platelet counts. These findings are worrisome for patients with both fungemia and thrombocytopenia. Mistakes in platelet count in thrombocytopenic patients may have dangerous consequences [16]. In a study by Branda and colleagues (2007) with the aim of investigating the effects of fungi on peripheral blood samples, the effects of three fungi *C. albicans*, *C. glabrata,* and *C. parapsilosis* on blood cell levels were evaluated using the peripheral blood counter ADVIA 120/2120 (Bayer HealthCare, Diagnostics Division, Tarrytown, NY). In their study, they concluded that these fungi increased platelet and WBC levels in a dose-dependent manner. They also stated that the presence of these fungi led to mistakes in identifying lymphocytes [1].

Kim and colleagues (2008) in a study evaluated the effects of *Staphylococcus aureus, Escherichia coli, C. albicans, C. tropicalis, C. krusei, C. dubliniensis, C. glabrata,* and *C. parapsilosis* on WBC counting using three counters ADVIA 120/2120, Sysmex-XE-2100 (TOA Medical Electronics, Kobe, Japan), and Coulter LH 750 (Beckman Coulter, Miami, FL, USA), the results showed that the presence of these microorganisms increased the levels of blood cells, especially WBCs. In addition, Sysmex-XE-2100 showed WBC levels significantly higher than the normal range in the presence of microorganisms, but this increase was not significant in two ADVIA 120/2120 and Coulter LH 750 devices [10]. These results indicate that blood contamination with *Candida* leads to changes in some blood variables in diagnostic tests. Failure to diagnose this co-infection along with the patient's illness may lead to mistakes in the treatment process. Supplemental tests and suspicion of this type of infection may be very helpful for patients who are likely to develop nosocomial infections, and their test results are not consistent with their bedside observations.

We would like to acknowledge a limitation in our study regarding the experimental design. To accurately determine the effectiveness of the Sysmex X S500i device in reducing measurement error in blood cells of patients with blood disorders and susceptibility to nosocomial infection, a proper experimental design including a control group is necessary. Unfortunately, the present study did not include a control group for comparison

purposes. The absence of a control group prevented us from directly comparing the effects of the Sysmex X S500i device on reducing measurement error. As a result, the interpretation and generalizability of the findings may be limited. Another limitation of this study is the lack of detailed information on the demographics, medical history, and current medical conditions of the participants. Complete blood samples of O- blood type were collected from the blood transfusion organization in Khorramabad in 2017 as the study population. However, not providing this additional information about the participants is a limitation that could potentially impact the accuracy and generalizability of the results. Future research should include comprehensive participant data to enhance the validity of the findings and provide a more comprehensive understanding of the relationship between blood cell counts and these factors.

Conclusion

The results of this study showed that fungal infections such as *Candida* infection could change the results of blood cell count. In the present study, the most affected variables were WBCs and platelets. In addition, changes in blood cells were more common in lymphocytes, monocytes, and neutrophils. Of the two devices examined in this study, the automated cell counter Sysmex X S500i showed less variation in the true levels of blood cells, including WBCs and platelets. This device seems to reduce measurement error in blood cells of patients who have blood disorders and are likely to develop nosocomial infections. A simple and quick method to prevent errors is to examine the peripheral blood smear using Wright staining, Giemsa staining, and so on to observe yeast agents, *Candida*, platelets, RBC, and WBC in the smear. Other methods such as blood culture, serology tests, and molecular tests are also recommended.

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Ethical permissions: This thesis was reviewed and approved by Lorestan University of Medical Sciences, Khorramabad, Iran (IR.LUMS.REC.1397.116) and is available on the website of Iran's National Ethics Committee in Biomedical Research.

Authors' contributions: Tarkhan F. (first author): original researcher/ discussion author; Aaliehpour A. (second author): original researcher/ methodologist/ discussion author; Sepahvand A. (corresponding author): supervisor, final reviewer.

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