Original Article

The Utility of Chest X-Ray Vs Computed Tomography in Febrile Neutropenic Patients Presenting to Oncology Unit of The Tertiary Care Hospital

Shaista Naz, Rabiha Manzoor*, Ifnan Shamraiz, Ayesha Bibi, Benish Hira, Ayesha Latif

Combined Military Hospital, Rawalpindi- Pakistan

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Corresponding Author
*Rabiha Manzoor
Combined Military Hospital, Rawalpindi- Pakistan
Email:rabihamanzoor364@gmail.com

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Abstract

Objective: Our study aimed at comparing the performance of high-resolution computed tomography (HRCT) and chest X-ray (CXR) in diagnosing febrile-neutropenic (FN) patients having childhood malignancies.

Methodology: This cross-sectional, prospective study included children having febrile neutropenia who had malignancies presenting at the pediatric oncology unit of Combined Military Hospital, Rawalpindi from 1st January 2022 to 30th June 2023. Total 114 children, up to 18 years having fever of 38.2°C or more and absolute neutrophil count <1000/µl, were included. Chest x-ray and HRCT were done to document the pulmonary lesions and findings were compared.

Results: CXR findings were normal in 64.9% and abnormal in 35.1%, while 84.2% had abnormal findings on HRCT and 15.8% were normal (p=0.001). HRCT findings were statistically significant in patients with ANC≤0.5 as compared to ANC >0.5 (p=0.005).

Conclusion: : HRCT is supercilious to CXR in determining pulmonic lesions in patients with febrile neutropenia. In severe neutropenic patients with fever, irrespective of respiratory symptoms, HRCT should be done. It can help to initiate timely proper treatment and reduce the morbidity and mortality.

Keywords: Child, Diagnostic imaging, Fever, Neoplasms, Neutropenia, Radiotherapy, Thoracic, X-ray, Computed tomography

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Introduction

Febrile neutropenia (FN) is a frequently occurring and potentially fatal problem in pediatric patients with malignancies. It can be a part of the disease process or it can result from the chemotherapy leading to myelosuppression.[1,2] The United Kingdom (UK) National Institute for Health and Care Excellence (NICE) defines FN as a temperature ≥38°C with an absolute neutrophil count (ANC) <500 cells/microliter (less than 0.5 x 10^9/L) or <1000/µL with an anticipated decline to <500/µL in the next 48-h period.[1,3] As ANC drops below 0.5 x 109/L there is a risk of very serious infections.[1] Neutropenia leads to development of various infections like pyogenic, fungal etc.[3] These infections are a main determining factor of morbidity and mortality in pediatric patients having malegnancies.[4] Mortality is 2 and 21% in untreated FN patients.1 Respiratory tract infections occur in 15% patients with febrile neutropenia. These patients usually present with fewer respiratory symptoms. Although chest x-ray is routinely done as a first line investigation along with other investigations. Most of the time, focus of the infections cannot be identified, despite the extensive workup. This this can be due the wide use of antibiotics as prophylaxis in these patients or the use of plain chest x-rays which has low sensitivity in detecting the chest lesions.[5,6] Radiographic findings become obvious as the neutrophil count increases as compared to low counts. Patients having febrile-neutropenia with chest infections, high-resolution computed tomography (HRCT) scans exhibit high sensitivity and specificity.[7,8] In patients having normal CXR with fever and neutropenia, HRCT can detect pulmonary lesions in 60% of such cases. Early identification of pulmonary lesion by HRCT can help in early treatment of the patients instead of CXR.[8,9]

The study was aimed at comparing the performance of HRCT and CXR and prompt diagnosis of lung abnormalities in patients having febrile neutropenia who had childhood malignancies.

Methodology

Study Design and place:

It's a prospective study carried-out in patients with febrile neutropenia (up to 18 years of age) with childhood malignancies attending the Pediatric oncology unit of Combined Military Hospital Rawalpindi 1st January 2022 to 30th June 2023. After taking Ethical approval from Institutional Review Board/ Ethical committee (Ser. No: 436). No specific sample size calculations were made for this study, and we included all patients fulfilling the inclusion criteria. Non-probability sampling technique was adopted. A total of 114 patients meeting the inclusion and exclusion criteria were enrolled consecutively. Those who were clinically and hemodynamically unstable or who had taken antibiotics within the previous two weeks were not allowed to participate in our study.

For the purpose of our study:

Fever: oral temperature ≥ 38.3°C once or a temperature ≥ 38°C extending over one hour.[10]

Neutropenia: An absolute neutrophil count (ANC) < 500 cells/mm3 or < 1000 cells/mm3 but anticipated to fall below to < 500 cells/mm3 in the next two days. Neutropenia is considered moderate when ANC is 500-1000 cells/mm3, severe when ANC 100-500 cells/mm3 and profound when ANC < 100 cells/mm^3.[1,11]

The patients' parents provided written informed consent. Data collected on excel sheet and then transferred to SPSS. CXR was done on all patient on arrival with fever and HRCT was done when fever not responded after 96 hours of empirical therapy. HRCT chest was done using 1.25- or 1-mm collimation at 10 mm intervals using a high frequency algorithm on a 4 slice (Light speed Qxi plus, GE medical systems, Milwaukee, WA) or a 16 slice (Somatom sensation 16, Siemens medical systems, Forscheim, Germany) CT scanner. Standard kVp (120) and mAs (200-250) were used. Senior and experienced radiologist interpreted the HRCT scans and chest x-rays findings. The investigations i.e, CBC, CRP, blood cultures, beta galactomanan etc., were collected. Clinical status and treatment details recorded. The criteria for a definitive diagnosis were blood culture results being positive, or improvement in clinical symptoms with specific medications.

Statistical Analysis:

Descriptive: categorical variables are expressed as frequencies and percentages, while continuous variables are shown as means ± SD or medians and interquartile range (IQR). Chi-squared and Fisher's exact tests were employed for categorical data, and Student's t-test and Wilcoxon Rank-sum test were utilized for continuous data. All tests were analyzed using SPSS 25. P-value ≤ 0.05 was considered significant. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of HRCT and CXR were calculated by contingency tables. Additionally, we want to compare both these imaging tools' sensitivities in our sample.

Results

A total of 114 patients, with 77 (67.5%) males and 37 (32.5%) females, up to 18 years were enrolled (table-4). Mean age was 6.29±4.11 years. ANC ≤ 500/ul was documented in 98 (86%) while ANC > 500/ul was reported in 16 (14%) (Table-4). Mean ANC was 0.27±0.21/ul. A great deal of individuals had hematological cancers 82 (71.9%) as compared to solid tumors 32 (28.1%) who developed febrile neutropenia during or after treatment (table-4). The most prevalent malignancy was Acute lymphoblastic leukemia (ALL), documented in 51(44.8%). Second most common malignancy was acute myeloid leukemia (AML) in 19 (16.7%). There were 12

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(10.6%) patients with hemophago-lympho-hystiocytosis (HLH) and 9 (7.9%) were Ewing Sarcoma (ES). Neuroblastoma (NB) and non-Hodgkin lymphoma (NHL) were documented in 7 (6.1%) each. Similarly, there were 3 cases of Wilms tumor (WT as well as of Germ cell tumors (GMT) constituting 2.6% each. 1 (0.9%) case was documented for each of Hepatoblastoma, osteosarcoma and retinoblastoma (Table-4). In addition to temperature, shortness of breath and cough were the predominant symptoms and tachypnea, crepitations and wheeze (on auscultation of chest) were most common signs besides fever.

Chest X-ray findings:

The majority of the patients' CXR 74 (64.9%) were unremarkable. The remaining CXR showed air space consolidation in 16 (14%), abnormal infiltrates in 11 (9.6%), pleural effusion in 6 (5.3%), nodules in 3 (2.6%), pneumothorax in 2 (1.8%) while cavitation and peribronchial cuffing observed in 1 (0.9%) CXR each. Those 74 patients who had normal chest radiographs, subsequent showed abnormalities on HRCT in 57 (77%) patients (table-2).

HRCT findings:

On HRCT, 97 (85.1%) patients exhibited unusual imaging findings. HRCT was normal in 17 (14.9%) (table-2). The most prevalent finding was consolidation documented in 30 (30.9%) cases, 17 were multifocal, 3 were multifocal with pleural effusion, 9 were unifocal and 1 was unifocal with air bronchogram. The second most frequent finding was nodules, found in 27 (27.8%) patients. Small nodules, measuring from 2 to 3 mm were documented in 20. Small nodules were centrilobular in distribution with tree-in-bud pattern in 1 case. Remaining were large nodules which were randomly distributed. A halo of ground glass opacity was seen around the nodules in 7 cases.

The third most common detection was Ground glass opacity (GGO) found in 24 (21.1%) patients. Bilateral diffuse GGO was seen in 10 cases. Cavitary lesions were seen in 4 (4.1%), one of these was thick walled. Effusion was present in 3 (2.6%), alveolar opacities in 2 (1.8%) , bronchiectatic changes in 1 (0.9%), bronchopneumonia in 1 (0.9%), bronchitis in 1 (0.9%), atelectasis in 1 (0.9%), hydropneumothorax in 1 (0.9%), and simple infiltrates 1 (0.9), Table-3 summarizes the findings on HRCT chest.

Findings on HRCT which were highly suggestive of specific respiratory infections in 89 patients. In 26 of these cases, ill- and well-defined nodules with spiculated margins were seen with a surrounding halo of GGO in 7 cases, air-crescent sign in 3, and remaining were scattered nodules and patchy foci. In all of these patients, a HRCT diagnosis of fungal pneumonia was suggested. BAL was not done due to invasive nature of the patients. Although blood cultures were negative but beta D-glactomanan levels were raised in 8 patients, in the remaining 19 cases, antifungal therapy was started based on the HRCT findings with favorable clinical response.

In 10 cases, HRCT showed interlobular and/or intralobular septal thickening with patchy or diffuse ground glass haze. In all these cases, a diagnosis of Pneumocystis jiroveci pneumonia (PCP) was suspected. These patients were treated empirically with cotrimoxazole and responded. Based on the HRCT findings of centrilobular nodules with tree-in-bud, appearance, consolidation and pleural effusion in varying combinations a diagnosis of tuberculosis was assumed in 4 cases. AFB and Mantoux test (MT) were negative in these patients.

Table 1. Frequencies of malignancies in patients with febrile neutropenia

S.No	Diseases	Frequency	n (%)
1.	Acute lymphoblastic leukemia (ALL)	51	44.8
2.	Acute myeloid leukemia (AML)	19	16.7
3.	Wilms Tumor (WT)	3	2.6
4.	Neuroblastoma	7	6.1
5.	Non-hodgkin Lymphoma (NHL)	7	6.1
6.	Retinoblastoma	1	0.9
7.	Hemophago-lympho-hystiocytosis (HLH)	12	10.6
8.	Ewing Sarcoma	9	7.9
9.	Hepatoblastoma	1	0.9
10.	Osteosarcoma	1	0.9
11.	Germ cell tumors	3	2.6
12.	Total	114	100

Table 2. Comparison of CXR and HRCT

Modality	Findings	Frequency N	Percentage %	P-value
CXR	Normal	74	64.9	0.001
	Abnormal	40	35.1	
	Total	114	100	
HRCT	Normal	17	14.9	
	Abnormal	97	85.1	
	Total	114	100	

Table 3. HRCT findings in patients

Findings	Frequency; N	Percentage; %
Alveolar opacities	2	1.8
Atelectasis	1	0.9
Bronchiectasis	1	0.9
Bronchitis	1	0.9
Bronchopneumonia	2	1.8
Cavitatory lesions	3	2.6
Consolidation	26	22.8
Consolidation with air bronchogram	1	0.9
Effusion	3	2.6
Effusion with consolidation	3	2.6
Ground glass opacities (GGOs)	24	21.1
Hydropneumothorax	1	0.9
Simple infiltrates	1	0.9
Nodular opacities suggestive of Aspergillosis	7	6.1
Nodular opacities	19	16.7
Thick walled cavitory lesions	1	0.9
Tree in bud appearance	1	0.9
Normal	17	14.9
Total	114	100

Based on HRCT findings and clinical findings, antitubercular therapy was given empirically with good response to therapy.

In 53 cases, bacterial infection was considered a first-choice diagnosis as based on unifocal or multifocal consolidation in 27 cases, associated pleural effusion was present in 3, GGO in 14, alveolar opacities in 2, cavitation in 4 cases, bronchopneumonia in 2, pulmonary infiltrates in 1.

Blood culture for bacterial growths were positive in 15 cases (staphylococci in 6 cases, Group A b hemolytic streptococci, pseudomonas aeruginosa and mycoplasma in 2 cases each, and 1 each for Klebsiella, acinobacter and serratia.).

Association of age and gender with the HRCT findings was statistically not significant (p value >0.05). Hematological malignancies as compared to solid tumors had a statistically significance with abnormal HRCT findings (p=0.000) similarly ANC ≤500/ul was significantly associated with abnormal HRCT findings (p=0.000) (table-4). Sensitivity HRCT in early detection pulmonary lesions

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Table 4. Patients characteristics

Parameter		HRCT findings		Total N (%)	P value
Gender	Males	9 (11.7)	68 (88.3)	77 (100)	0.083
	Females	9 (24.3)	28 (75.7)	37 (100)	
Age	<5	9(19.6)	37(80.4)	46(100)	0.495
	5-10	5(10.9)	41(89.1)	46(100)	
	>10	3(13.6)	19(86.4)	22(100)	
Malignancies	Hematological	4(4.9)	78(95.1)	82(100)	002
	Solid tumors	13(40.6)	19(59.4)	32(100)	
Absolute neutrophil count	≤500	10(10.2)	88(89.8)	98(100)	0.006
		7(43.8)	9(56.3)	16(100)	

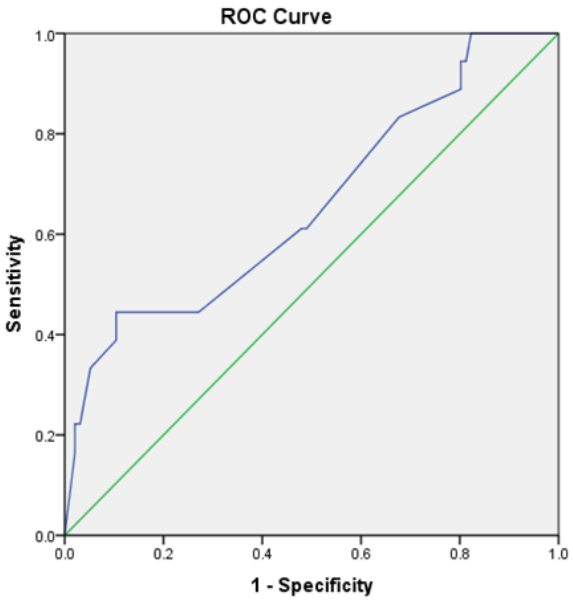

Figure 1: absolute neutrophil count in predicting radiographic active pulmonary infection (AUC=0.659)

in childhood malignancies is 80% and specificity is 76% with positive predictive value (PPV) of 95% and negative predictive value (NPV) 40%, whereas Sensitivity of CXR is 70% and specificity 25% with PPV of 63% and NPP of 31%. ROC analysis shows that the absolute neutrophil count was useful for predicting radiographic active pulmonary infection (AUC=0.659). ANC less than 0.15/uL at 95%, CI (0.513-.805) was 83.3 sensitive and 67.7 specific (Figure 1).

Discussion

In malignancies, pulmonary infections are the most devastating complications reported during neutropenia phase.[12] Due to the subtle and impaired inflammatory response, pulmonary infections can present even without symptoms and signs except fever which may be the only presenting sign.[13] Febrile neutropenia is an oncological emergency and a dreadful complication of chemotherapy.[8,13] Pulmonary infections required prompt diagnosis and early treatment as mortality can reach up to 20%. Normally chest x-rays are commonly performed in these patients along with other baseline investigations.[7,8,13] However CXR has low sensitivity in detecting the pulmonary lesions.[5,6] HRCT is superior to CXR in detecting the pulmonary lesions as it has high sensitivity.[5,6,7,8] Pulmonary infections were encountered in 60% of FN patients on HRCT with normal CXR.[6] This study focused on the comparison of HRCT and CXR in detecting the pulmonary lesions in febrile neutropenic pediatric patients.

In present study febrile neutropenia was documented in 71.9% hematological malignancies as compared to solid tumors in 28.1%. A study by Geen et al. documented FN in 54% hematological malignancies and in 46% solid tumors.14Acute lymphoblastic leukemia (ALL) was the most common malignancy in 51(44.8%) patients, documented in current study results which have similar to 48 (34.8%) findings by Zaleska-Dorobisz et al.15 AML was second most common malignancy in 31(22.5%) in the study Zaleska-Dorobisz et al., similar to 19 (16.7%) patients in this study.15 Similarly ALL was also the most common malignancy in 15 29%) patients with FN in a research by Green et al., followed by AML in 9 (24%).[15]

According to current research, CXR was normal in 74 (64.9%) and abnormal in 40 (35.1%). The result was similar to a study by Kang et al., in which 71 (68.26%) CXR were normal in patients with FN and abnormal in 33(32%), however this study was performed on adult patients.[8] Similarly a study conducted on 138 pediatric patients by Zaleska-Dorobisz et al., with FN, 80 (57.97%) had normal CXR, while abnormal findings on CXR were present in while 58 (42.03%).[15] While on HRCT 97 (85.1%) patients showed abnormal imaging findings according to this study with normal in 17 (14.9%), these

findings were comparable with the study done by Kang et al., in which pulmonary abnormalities were detected in 93 patients (89.4%), and no lesion was documented in 11 (10.57%).[8] Similarly CT scan showed pulmonary lesions in 116 (84.06%) of the 138 patients in study by Zaleska-Dorobisz et al. while it was normal in 22 (15%) cases.[15] Similarly it was shown by Majzoub at al that 30% patients had no abnormality detected on CXR, while those all were positive on HRCT.[16] All these three studies concluded that CT scan is superior to CXR in diagnosing the pulmonary lesions in FN patients and is fruitful in early diagnosis and management.[8,15,16]

Age and gender were not statistically associated with HRCT findings ($p<0.05$) similar to the findings by Majzoub et al. and Green at el.[5,15] In contrast to current research findings, ANC was not significantly associated with HRCT findings, in a study by Sricharoen et al.[17]

Consolidation was the commonest finding (30.9%), our study, followed by nodular opacities (27.8%) and GGOs (21.1%), similar to the studies by Kang et al., Gerritsen et al [8,18] However GGOs were the most common finding in a study by Zaleska-Dorobisz et al.[16] Bacterial infections were the most common, followed by fungal, PCP and Tuberculosis in our study similar to the Kang et al., Gerritsen et al. and Zaleska-Dorobisz et al.[8,16,18]

Sensitivity of HRCT for prompt diagnosis of lung lesions in childhood malignancies is 80% and specificity is 76% with positive predictive value (PPV) of 95% and negative predictive value (NPV) 40%, whereas Sensitivity of CXR is 70% and specificity 25% with PPV of 63% and NPP of 31%. A study by Burivong et al., found that the sensitivity, specificity, PPV, and NPV of CXR in timely detection of lung infections using radiology were 50%, 74%, 61%, and 64%, respectively and for HRCT sensitivity, specificity, PPV, and NPV 91%, 40%, 53%, and 86%, were respectively.[17] Similarly Gerritsen et al., concluded that HRCT had higher sensitivity as compared to CXR in early detection of pulmonary lesions in FN patients.[18]

Although this study shows that HRCT is the best imaging modality in early recognition of lung abnormalities in febrile-neutropenic patients in childhood malignancies, however it is costly along with risk of radiation exposure and not easily available in every setup. As this is the first study from Pakistan, so further studies should be done.

Conclusion

In patients with febrile neutropenia HRCT is an excellent modality and superior to CXR in the diagnosis of early pulmonary infections. It is very useful for early diagnosis and thorough description of problems in the lungs which can be easily missed on CXR. So, can help in the timely diagnosis and management of the patients having febrile-neutropenia. This can reduce the duration of stay at hospital, rates of admissions in intensive care unit, and the number of diagnostic procedures required.

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Authors' Contribution Statement

SN contributed to the conception, design, acquisition, analysis, interpretation of data, drafting of the manuscript, critical review of the manuscript, and final approval of the version to be published. RM contributed to the acquisition, analysis, interpretation of data, drafting of the manuscript, and critical review of the manuscript. IS contributed to the acquisition, analysis, interpretation of data, and drafting of the manuscript. AB contributed to the acquisition, analysis, interpretation of data, and drafting of the manuscript. BH contributed to the acquisition, analysis, interpretation of data, and drafting of the manuscript. AL contributed to the acquisition, analysis, interpretation of data, and drafting of the manuscript. All authors are accountable for their work and ensure the accuracy and integrity of the study.

Conflict of Interest

Authors declared no conflict on interest

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None

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.