JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

*Original Article*

# The utility of chest X-ray *vs*. computed tomography in febrile neutropenia patients presenting to the emergency department

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## Abstract

Introduction: Pulmonary infections are not uncommon in patients with febrile neutropenia. Physicians have agreed to perform a chest X-ray (CXR) for all febrile neutropenic patients presenting with respiratory signs/symptoms. Nevertheless, they were divided into two groups when it came to asymptomatic febrile neutropenic patients (i.e. without respiratory signs/symptoms). A superior alternative to CXR is Computed Tomography (CT). CT, in comparison to CXR, was shown to have better sensitivity in detecting pulmonary foci. The aim of our study is to compare the diagnostic performance of CT and CXR in febrile neutropenic patients presenting to the emergency department, regardless of their clinical presentation. We are also interested in the predictors of pneumonia on chest imaging.

Methodology: This is a retrospective cohort study conducted on febrile neutropenic adult cancer patients presenting to the emergency department of the American University of Beirut Medical Center.

Results: 11.4% of 263 patients had pneumonia although 27.7% had respiratory signs/symptoms. 17.1% of those who were symptomatic and did a CXR were found to have pneumonia. 41.7% of those who were symptomatic and did a CT were found to have pneumonia. 30% had negative findings on CXR but pneumonia on CT.

Conclusion: Patients with positive findings of pneumonia on chest imaging mainly had solid tumors, profound neutropenia, a higher CCI and a longer LOS. The presence of respiratory signs is the main predictor of positive pneumonia on chest imaging. CT is superior to CXR in detecting pulmonary foci in the population studied.

**Key words:** Chest X-ray; computed tomography; emergency department; febrile neutropenia; respiratory signs and symptoms.

*J Infect Dev Ctries* 2020; 14(10):1178-1184. doi:10.3855/jidc.12577

(Received 21 February 2020 – Accepted 26 May 2020)



## Introduction

Neutropenic fever has been widely described in the literature as one of the most critical oncologic complications, particularly encountered in the setting of the Emergency Department (ED). An estimated overall mortality of 7.25 % and 12.5 % has been recorded in solid and hematological tumor patients, respectively [1-4]. While mortality in this population is due to countless factors, infection remains one of the most common causes leading to up to 5 % mortality in this population [4-6]. Despite being comprehensively worked up, 44% of these patients do not have a focus of infection identified [7]. This could either be due to the use of prophylactic antimicrobial therapy in the population under study [8-10] or due to the low sensitivity of plain chest radiographs that are commonly performed in the ED [11]. No matter what the cause of inability or delay to detect the focus of infection is, it puts patients from a vulnerable population into further risks and complications [12].

Pulmonary infections are not uncommon in patients with febrile neutropenia. Consequently, guidelines were set to harmonize the management of such patients. However, we still do not have one established protocol. Physicians have agreed to perform a chest X-ray (CXR) for all febrile neutropenic patients presenting with respiratory signs/symptoms. Nevertheless, they were divided into two groups when it came to febrile neutropenic patients that are asymptomatic (i.e. without respiratory signs/symptoms) upon presentation [13]. ESMO guidelines stress the importance of performing a CXR in all febrile neutropenic patients, whereas IDSA guidelines are a bit more restrictive and only advise CXR in those presenting with respiratory signs/symptoms [14].

In the recent years, there has been increased awareness of medical personnel to such patients. The

cruciality of detecting infections in patients of such a vulnerable population became a priority within the setting of the ED. As a result, an alternative to CXR but a superior diagnostic tool has been put on the table: Computed Tomography (CT). CT is either high resolution (HR) or low resolution (LR) [13]. HRCT was proven to detect pulmonary abnormalities in 60% of febrile neutropenic patients who have had a normal CXR [15,16]. Nonetheless, HRCT has not been implemented as part of the initial diagnostic workup of febrile neutropenia due to its high cost and radiation doses [17]. Low Dose- CT (LDCT), in comparison to CXR, was shown to have better sensitivity in detecting pulmonary foci [18,19].

The primary aim of our study is to compare the diagnostic performance of LDCT and CXR in febrile neutropenic patients presenting to the ED, irrespective of their clinical presentation (with/without respiratory signs/symptoms). We are also interested in the clinical predictors of pneumonia on chest imaging.

## Methodology

*Study Design and Setting*

This is a retrospective cohort study conducted on febrile neutropenic adult (>18 years of age) cancer patients presenting to the ED of the American University of Beirut Medical Center (AUBMC) between January 2013 and September 2018. AUBMC is an over 350-bed hospital with more than 55,000 yearly ED visits. Ethical approval was obtained from the Institutional Review Board at AUBMC under the protocol number (BIO-2018-0455).

*Study Population*

We included all adult (> 18 years old) patients who presented to the ED of AUBMC with febrile neutropenia. We only took each patient's first visit for febrile neutropenia into consideration. Those who were not admitted, who received antibiotics within the last two weeks or who were clinically and/or hemodynamically unstable were excluded from our study. We also excluded those who did not have a CXR or a CT scan done in the ED.

For the purposes of our study:

- Fever: oral temperature ≥ 38.3°C once or a temperature ≥ 38°C extending over one hour[14].
- Neutropenia: an absolute neutrophil count (ANC) < 500 cells/mm$^3$ or < 1000 cells/mm$^3$ but anticipated to fall below to < 500 cells/mm$^3$ in the next two days.
    - Neutropenia is considered moderate when ANC is 500-1000 cells/mm$^3$, severe when ANC 100-500 cells/mm$^3$ and profound when ANC < 100 cells/mm$^3$.
- Pneumonia: the diagnostic criterion includes a *clinical presentation* suggestive of pneumonia (cough, dyspnea, rhinorrhea, pleuritic chest pain, fever, tachycardia, altered mental status), *lung examination findings* of decreased breath sounds and crackles, and *chest imaging* (CT, CXR) showing infiltrates [20].

*Statistical Analysis*

Descriptive and bivariate statistics were conducted on the two groups of positive and negative pneumonia (by either CXR or CT) with continuous variables presented as means ± SD or medians and interquartile range (IQR) and categorical variables expressed as frequencies and percentages. Student's t-test and Wilcoxon Rank-sum test were used for continuous data while Chi-squared and Fisher's exact tests were used for categorical data. All tests were interpreted at alpha of 0.05.

**Table 1.** Baseline Characteristics of Patients with and without Pneumonia (by either CT or CXR).

| Variable | | All (N = 263) | Positive pneumonia (N = 30) | Negative pneumonia (N = 233) | P-value |
|---|---|---|---|---|---|
| Age (mean ± SD) | | | 50.97 ± 8.89 | 49.00 ± 18.32 | 0.581 |
| Gender (Female) | | 126 (47.9) | 10 (33.3) | 116 (49.8) | 0.090 |
| Tumor type | Solid | 121 (46.2) | 15 (51.7) | 106 (45.5) | |
| | Liquid | 132 (50.4) | 12 (41.4) | 120 (51.4) | 0.391 |
| | BMT | 9 (3.4) | 2 (6.9) | 7 (3.0) | |
| ANC (Median (IQR)) | | | 0 (0,96) | 0 (0,208) | 0.551 |
| Neutropenia | Moderate | 21 (8.0) | 1 (3.3) | 20 (8.6) | |
| | Severe | 59 (22.4) | 6 (20.0) | 53 (22.8) | 0.535 |
| | Profound | 183 (69.6) | 23 (76.7) | 160 (68.7) | |
| CCI (Median (IQR)) | | | 3.5 (2,5) | 3 (2,5) | 0.551 |
| LOS (Median (IQR)) | | | 6 (4,8) | 4 (3,7) | 0.042 |

CCI: Charlson Comorbidity Index; predicts 10-year survival in patients with multiple comorbidities; LOS: Length of stay in days.

**Table 2.** CXR and CT findings in positive and negative respiratory symptoms.

| Variable | | Positive Respiratory Symptoms (N = 73) | Negative Respiratory Symptoms (N= 190) | P-value |
|---|---|---|---|---|
| CXR Done | Yes | 70 (95.9) | 185 (97.4) | 0.689 |
| | No | 3 (4.1) | 5 (2.6) | |
| CXR pneumonia | Positive | 12 (17.1) | 9 (4.9) | 0.001 |
| | Negative | 58 (82.9) | 176 (95.1) | |
| CT Done | Yes | 12 (16.4) | 29 (15.3) | 0.814 |
| | No | 61 (83.6) | 161 (84.7) | |
| CT pneumonia | Positive | 5 (41.7) | 6 (20.7) | 0.247 |
| | Negative | 7 (58.3) | 23 (79.3) | |

**Table 3.** Predictors of Negative/Positive CXR in Patients with Positive CT for Pneumonia.

| Variable | | Positive CXR pneumonia (N = 21) | Negative CXR pneumonia (N = 234) | P-value |
|---|---|---|---|---|
| Age mean ± SD | | 51.29 ± 21.37 | 49.14 ± 18.11 | 0.608 |
| Gender: female | | 8 (38.1) | 114 (48.7) | 0.351 |
| Respiratory symptoms | Yes | 12 (57.1) | 58 (24.8) | 0.001 |
| Tumor type | Solid | 10 (50.0) | 109 (46.6) | |
| | Liquid | 8 (40.0) | 119 (50.9) | 0.156 |
| | BMT | 2 (10.0) | 6 (2.6) | |
| ANC Median (IQR) | | 0 (0,180) | 0 (0,192) | 0.899 |
| Neutropenia | Moderate | 0 (0.0) | 19 (8.1) | |
| | Severe | 6 (28.6) | 50 (21.4) | 0.437 |
| | Profound | 15 (71.4) | 165 (70.5) | |
| CCI median (IQR) | | 5 (2,6) | 3 (2,5) | 0.236 |
| LOS median (IQR) | | 6 (4,6) | 4 (3,7) | 0.149 |

**Table 4.** 2×2 Table of CXR Compared to CT (gold standard).

| Variable | | Pneumonia on CT (N = 11) | No pneumonia on CT (N = 22) |
|---|---|---|---|
| Pneumonia on CXR | Yes | 2 | 1 |
| | No | 9 | 21 |

**Table 5.** Sensitivity and Specificity for CXR vs. CT in Predicting Pneumonia.

| Statistic | Value | 95% CI |
|---|---|---|
| Sensitivity | 18.18 | 2.28-51.78 |
| Specificity | 95.45 | 77.16-99.88 |
| Positive predictive value | 66.67 | 16.86-95.18 |
| Negative predictive value | 70.00 | 63.51-75.78 |

Descriptive analysis is performed to determine the factors that might predict development of pneumonia in adult cancer patients with febrile neutropenia. Through this analysis, we aim to ascertain whether or not respiratory signs/symptoms are sufficient to decide if a patient should undergo chest imaging (CXR and/ or CT scan). We also aim to compare the sensitivities of these two imaging tools in our population.

Analysis was conducted using STATA MP Version 13.0 (College Station, TX: Stata Corp LP).

## Results

*Characteristics of Patients*

A total of 924 patients were screened of which 263 met the inclusion criteria and were included in our study. Slightly less than half (47.9%) the population were females. 46.2 % had solid tumors, 50.4% had liquid tumors and 3.4% have undergone bone marrow transplantation (BMT). Also, the majority of the patients (69.6%) had profound neutropenia, 22.4% had severe neutropenia and only 8% had moderate neutropenia (Table 1).

Of the total, only 30 patients (11.4 %) were positive for pneumonia. 33.3% of those who had pneumonia (by either CXR or CT) were females and their mean age was 50.97 ± 18.89. Those who were positive for pneumonia mainly had solid tumors (51.7%), followed by liquid tumors (41.4 %). Only 6.9 % have undergone BMT. More than three-quarters (76.7%) of the those with pneumonia had profound neutropenia. Also, the median Charlson Comorbidity Index (CCI) was of 3.5 and the median LOS was of 6 days in the patients that were found to have pneumonia.

*Chest Imaging Results*

Of the total number of patients included in the study, 73 patients (27.7 %) had respiratory signs/symptoms upon presentation (i.e.: cough, dyspnea, rhinorrhea, pleuritic chest pain) and the rest were asymptomatic.

CXR was done in 95.9% of those who had respiratory signs/symptoms. 17.1% of those who had respiratory signs/symptoms and had a CXR done were found to have pneumonia on CXR (16.4% of all those who had respiratory signs/symptoms), while only 4.9% of those who did not have respiratory signs/symptoms but had a CXR done were found to have pneumonia on CXR (4.7% of all those who had no respiratory signs/symptoms).

CT was done in 16.4% of those who had respiratory signs/symptoms. 41.7% of those who had respiratory signs/symptoms and had a CT done were found to have pneumonia on CT (6.8% of all those who had respiratory signs/symptoms), whereas 20.7% of those who did not have respiratory signs/symptoms but had a CT done were found to have pneumonia on CT (3.1% of all those who had no respiratory signs/symptoms).

21 patients (8%) had positive CXR regardless whether they had or not respiratory signs/symptoms. The mean age for those who had a positive CXR was 51.29 ± 1.37 with 38.1% being females and 57.1% having respiratory signs/symptoms. 50% had solid tumors, 40% had liquid tumors and 10% have undergone a BMT. Patients that were found to have pneumonia on CXR were mostly profoundly neutropenic (71.4%) with a median CCI of 5 and a median LOS of 6 days (Tables 2 and 3).

*CXR vs. CT Sensitivity Analysis for Detecting Pneumonia*

Out of the 30 that had pneumonia, 9 (30%) were actually found to have negative findings on CXR but a diagnosis of pneumonia was made based on CT results. Based on these results, CXR, compared to CT, was found to have a sensitivity of 18.18% (95% CI 2.28-51.78), specificity of 95.45% (95% CI 77.16-99.88), negative predictive value of 70.00% (95% CI 63.51-75.78) and a positive predictive value of 66.67 (95% CI 16.86-95.18) (Tables 4 and 5).

## Discussion

Febrile neutropenia is a priority in the ED and patients of this population should be given immediate medical attention. Their augmented liability to contract infection has put them at stake. However, consequences can still be prevented by timely management after thoroughly examining and investigating in attempt to find a focus of infection. Among the common causes of infection in such a population is respiratory tract infection. There has been consensus to obtain chest imaging in all of those with febrile neutropenia that present with respiratory signs/symptoms. The dilemma however lies in those that have neutropenic fever but present to the ED without any signs/symptoms indicative of a respiratory tract infection: ESMO guidelines advise obtaining a CXR in all adult febrile neutropenic patients; on the other hand, IDSA guidelines advise a CXR only in those that are symptomatic (have respiratory signs/symptoms) [2,14]. Moreover, it has been widely described that CXR is the first diagnostic test in all candidates for chest imaging, especially in the setting of the ED. However, to make accurate and timely diagnosis by rapidly detecting the

focus of infection, alternative diagnostic tools must be investigated [13,15].

We conducted a comprehensive retrospective chart review to assess the value of chest imaging in adult febrile neutropenic patients presenting to our ED regardless of their clinical presentation and to compare the sensitivities of the two most widely used chest imaging tools: CXR *vs*. CT scans.

Our study is the first in the region, to our knowledge, to evaluate the cruciality of obtaining chest imaging in febrile neutropenic patients presenting without signs/symptoms of respiratory tract infection. We, as well, aim to assess the value of CT in comparison to CXR as means to make fast but accurate diagnoses in such a vulnerable population.

In our study, those who were positive for pneumonia mainly had solid tumors (51.7%) and more than three-quarters (76.7%) had profound neutropenia. On the other hand, those that did not have pneumonia were relatively younger with a mean age of 49.00 ± 18.32, mostly had liquid tumors (51.4%), but also mostly had profound febrile neutropenia (68.7%). It is of importance to note that those with pneumonia had a higher CCI and a longer LOS compared to those who were negative for pneumonia (3.5 (2,5) *vs*. 3 (2,5) and 6 (4,8) *vs*. 4 (3,7), respectively).

This leads us to the conclusion that having a solid tumor, a higher CCI and a longer LOS ($p = 0.042$) might predict pneumonia in this population.

In our study, 27.7 % of the patients had respiratory signs/symptoms upon presentation (i.e.: cough, dyspnea, rhinorrhea, pleuritic chest pain) while the rest were asymptomatic. CXR was done in 95.9% of those who had respiratory signs/symptoms. 17.1% of those who had respiratory signs/symptoms and had a CXR done were found to have pneumonia on CXR, while only 4.9% of those who did not have respiratory signs/symptoms but had a CXR done were found to have pneumonia on CXR. CT was done in 16.4% of those who had respiratory signs/symptoms. 41.7% of those who had respiratory signs/symptoms and had a CT done were found to have pneumonia on CT, whereas 20.7% of those who did not have respiratory signs/symptoms but had a CT done were found to have pneumonia on CT.

This tells us that respiratory signs/symptoms might help orient emergency physicians to those that are at a higher risk for pneumonia and are thus candidates for chest imaging (CXR/CT); however, it is not sufficient as the sole predictor for pneumonia on chest imaging.

8% of our population had positive CXR regardless whether or not they had respiratory signs/symptoms. The mean age for those who had a positive CXR was 51.29 ± 21.37 with 38.1% being females and 57.1% having respiratory signs/symptoms. 50% had solid tumors, and 71.4% were profoundly neutropenic, with a median CCI of 5 and a median LOS of 6 days.

Among all aforementioned factors, the presence of respiratory signs/symptoms has been proven as the main predictor for having pneumonia on a CXR ($p = 0.001$).

30% of those that had pneumonia were actually found to have negative findings on CXR, but a diagnosis of pneumonia was made based on CT results. Based on this, CXR, compared to CT, was found to have a sensitivity of 18.18% (95% CI 2.28-51.78), specificity of 95.45% (95% CI 77.16-99.88), negative predictive value of 70.00% (95% CI 63.51-75.78) and a positive predictive value of 66.67 (95% CI 16.86-95.18).

This shows a limited sensitivity of CXR in detecting pulmonary foci when compared to CT [11].

All conclusions made in our paper are in line with what has been previously published in the literature and comes to confirm the external validity and the reproducibility of our results.

A previous study has shown a 7.5% increase in detection rate when they used a CT instead of a CXR. As CT of the chest is the known gold standard for detection of pulmonary infections, this slight rise is not considered significant. This insignificant increase was attributed to a low number of pulmonary infections in their population [13,16]. However, this same study proved a statistically significant amplified sensitivity of CT (73%) when compared to a CXR (36%) [13].

Another retrospective study included 1083 adult febrile neutropenic patients that have undergone stem cell transplantation. In this study, a CXR was done on 318 patients: out of the 242 CXRs done on asymptomatic patients, a 100% were negative and out of 76 done on patients with respiratory signs/symptoms, 31.6% showed pneumonia [11]. This shows that the presence of respiratory signs/symptoms is a good predictor for pulmonary infection.

Two published studies have also compared the value of CXR to CT in patients with neutropenic fever and came to the conclusion of CT being superior to CXR. In the first study, patients were those that have acute myelocytic leukemia and are febrile neutropenic with signs/symptoms of respiratory tract infection [19]. It was found out that 77.5% of their population had pneumonia on CXR when in fact 95% had pneumonia on CT. Therefore, 17.5% of pneumonia cases were missed by a CXR [19]. In the other study, patients were

those that had febrile neutropenia for more than two days. In their population, chest imaging was obtained irrespective of the clinical presentation (symptomatic and asymptomatic). 72% patients were diagnosed with pneumonia with respective sensitivities of 39% for CXR and 63% for CT [18].

## Limitations

Limitations of our study should be well-stated despite its uniqueness in the region. Our study is a single-institutional review with a very narrow sample size (only 30 patients had pneumonia). Moreover, the retrospective nature of our study enforces some resource restrictions along with data inaccessibility. Also, some respiratory signs/symptoms (cough, dyspnea, rhinorrhea, pleuritic chest pain) are mostly imperceptible in the population we are studying [21]. Besides, we involved patients with short periods of neutropenia along those that have prolonged neutropenia; this might have influenced the incidence of pulmonary infections since longer periods of neutropenia predispose patients to pneumonia.

## Conclusion

The incidence of pulmonary infections in adult cancer patients with febrile neutropenia is not uncommon and the presence of respiratory signs/ symptoms may not always be evident. Physicians have agreed to obtain chest imaging in all febrile neutropenic patients that are symptomatic. In asymptomatic febrile neutropenic patients, this is still controversial. In our study conducted on febrile neutropenic patients, we found that patients with positive findings of pneumonia on chest imaging mainly had solid tumors, profound neutropenia, a higher CCI and a longer LOS. We also concluded that the presence of respiratory signs is a main predictor of positive pneumonia on chest imaging. At last, we were able to prove that CT is superior to CXR in detecting pulmonary foci in the population studied.

The first diagnostic tool in the setting of the ED is usually the CXR. However, several studies, including ours, have successfully proven a greater sensitivity of CT for detecting pulmonary foci in such a population. It is undoubtfully true that CT scans will impose instant greater costs on patients and the healthcare system; however, on the long run, early diagnosis and management will reduce expenses by decreasing length of stay, rate of readmissions, intensive care unit admissions and the amount of investigations done (i.e.: instead of obtaining an inconclusive CXR and then going to CT in this population, physicians can directly obtain a CT). This will save time, effort and resources.

Further prospective studies that include larger sample sizes are required to ascertain our results and their generalizability.

## Authors' Contributions

All authors equally contributed to this work. IEM, HZ and AEZ were responsible for conceptualization, formal analysis, methodology, project administration, supervision, validation and visualization. RC and MAC were responsible for conceptualization, data curation, formal analysis, investigation, resources, original draft writing, and review and editing. MAK was responsible for conceptualization, formal analysis, investigation and resources. RK was responsible for data curation, formal analysis, investigation and resources.

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**Conflict of interests:** No conflict of interests is declared.