Original Article

Correlation Between PET/CT Maximum Standard Uptake Value and NLR in Malignancy Patients Pre- and Post-Treatment

PET/CT and NLR before and after treatment with different Malignancy

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ABSTRACT

Objective: To determine relationship in-between uptake of FDG and NLR (neutrophil-lymphocyte ratio), which is an indicator of systemic inflammation, both prior to treatment as well as after treatment in various solid and hematological cancers.

Study Design: comparative cross sectional observational study

Place and Duration of Study: This study was conducted at the at Clifton and North campus of Dr Ziauddin University for 1 year (March 2022 to February 2023.

Materials and Methods: This study using non-probability purposeful sampling was done. Cancer patients >18 years of age, having definitive diagnosis of malignancy, consenting for pre-therapeutic FDG-PET/CT imaging and differential blood analysis done were included. SPSS version 23.0 was used. For quantitative variables mean and IQR were reported while for qualitative variables were recorded as frequency and percentages. Stratification was carried our before and after treatment by applying chi-square test keeping p-value <0.05 as statistically significant.

Results: From 237 patients with mean age 52.47 ± 15.5 years, 147 (62%) females and 90 (38%) males. Diagnosis of lymphoma was reported in 72 (30.4%) of patients. A significant difference was observed in the pre and post treatment values of SUV max (p-0.01), NLR (p-0.04), C-reactive protein (p-0.03) and ESR (p-0.04). Majority of patients included were females (62 %) with the highest diagnosis being of lymphoma (30.4%) while least common diagnosis was of sarcoma and melanoma in 0.84 % of patients each.

Conclusion: Both SUV max uptake of PET/CT imaging and NLR showed significant decrease after treatment of cancer patients.

Key Words: Maximum Standard Uptake, Positron Emission Tomography, Computed Tomography, Neutrophil to Lymphocyte Ratio, Cancer

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INTRODUCTION

Cancer, one of the leading causes of mortality and single most important barrier towards increase in life expectancy throughout the globe in 21st century[1]. World Health Organization has estimated cancer to be 1st or 2nd leading reason of death before 70 years in 91 countries while 3rd or 4th in additional 22 countries. The reason behind cancers is complex, reflecting both aging and substantial populations' growths[2].

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Positron emission tomography/computed tomography (PET/CT), an imaging modality which is widely used for diagnosing, staging as well as in assessing therapeutic responses in the field of oncology[3]. The radiolabeled deoxy-2-[18F] fluro-D-glucose (1F-FDG) is an analogue of glucose, used as standard tracer for evaluation of neoplastic tissues. The value of standardized uptake (SUV) is termed as semi-quantitative parameter used for measuring accumulation of tracers in tissues, especially as in tumor glucose metabolism[4]. SUV max is accepted to be the most widely used metric due to its accuracy as well as simplicity in applying to clinical practice. The association in-between tumor 18F-FDG uptake and systemic inflammatory responses (SIR) has become of interest in several malignancies[5].

Inflammation related to cancer is one of the hallmarks of cancer, wherein inflammatory cells and mediators are some essential elements of tumor micro-environment. The inflammatory responsible tends to be detectable only in the peripheral films, the evidence being neutrophilia with or without lymphopenia[6].

Furthermore, neutrophil to lymphocyte ratio (NLR), which derives it from two factors, absolute neutrophil and absolute lymphocyte count, is prognostically used to assess outcome of patients in various tumors[7].

A high NLR is reported to be independent prognostic factor in various advance cancers having variable NLR thresholds, for instance in colorectal and pancreatic cancer the NLR is observed to be >5, in advanced gastric cancer (NLR >2.5), metastatic renal cell carcinoma and prostatic cancer (NLR >3), advanced ovarian cancer (NLR >2.60), advanced cervical cancer (NLR >1.9) and in nasopharyngeal carcinoma (NLR >2.5) (8-13).

The use of NLR as a prognostic utility and as marker of systemic inflammation in under-studied in many studies related to PET/CT as well as scarce data is available locally with regards to both use of PET/CT and NLR before and after treatment in various malignancies[14]. Studies have reported the use of SUV max uptake and NLR to be associated with tumor prognosis, a high level of both being linked to poor prognosis[15]. Thus this study evaluated pre-therapeutic neutrophil-to-lymphocyte ratio (NLR) with tumor metabolism marker 18-fluorodeoxyglucose positron emission tomography/ computed tomography (FDG-PET/CT) and compared their levels with post-therapeutic NLR and SUV max.

The objective of this research was to determine relationship in-between uptake of FDG and NLR (neutrophil-lymphocyte ratio), which is an indicator of systemic inflammation, both prior to treatment as well as after treatment in various solid and hematological cancers. We hypothesized that patients having high SUV max as well as high NLR were associated with a poor prognosis.

MATERIALS AND METHODS

This comparative cross sectional observational study was carried out at the Clifton and North campus of Dr Ziauddin University for a period of 1 year after approval of synopsis by the ERC (from March 2022 to February 2023). The sampling technique used was non-probability purposeful sampling. Cancer patients >18 years of age, having a definitive diagnosis of malignancy, consenting for pre-therapeutic FDG-PET/CT imaging and having differential blood analysis done were included in the study while patients having either an acute infection, active inflammatory condition, incomplete clinical information or refusing to consent for the study were excluded.

Data Collection Procedure: After ethical approval from the Ethical Review Committee of Dr Ziauddin University Hospital Karachi, the study commenced. All patients receiving treatment at either Clifton or North campus of Dr Ziauddin University Hospital fulfilling the inclusion criteria were included in the research. Demographics of patients, SUV max and SUV mean, total leucocyte count (including neutrophils and lymphocytes), neutrophil to lymphocyte ratio (NLR), LDH, CRP, ESR serum albumin and provisional diagnosis were all recorded.

Data Analysis: For data analysis, SPSS version 23.0 was used. For quantitative variables such as age hematological parameters, SUV mean and SUV max, mean and IQR were reported while for qualitative variables such as provisional diagnosis of cancer were recorded as frequency and percentages. Stratification was carried our regarding SUV max uptake and NLR before and after treatment for seeing effect of such modifiers on outcome variables by applying chi-square test keeping p-value <0.05 as statistically significant.

RESULTS

A total of 237 patients were included in the study with mean age of 52.47 ± 15.5 years and with 147 (62 %) females and 90 (38 %) males. Diagnosis of lymphoma was reported in 72 (30.4 %) of patients followed by gynecological tumors in 43 (18.1 %) of patients. Zero positive lymph nodes were reported in 114 (48.1 %) of patients, 1-3 in 45 (19 %) of patients, 4-9 in 36 (15.2 %) of patients, >10 in 24 (10.1 %) of patients while in 18 (7.6 %) they were unknown. Metastasis was reported in 93 (39.2 %) of patients. Regarding TNM staging, stage 1 was found in 19 (8 %) of patients, stage 2 in 62 (26.3 %) patients and stage 3 in 53 (22.4 %) of patients. Lymphovascular invasion was seen in 130 (54.9 %) of patients overall [Table 1].

The mean and Inter-Quartile Range (IQR) of SUV max before treatment was 10.35 (5.8-12.84) while after treatment was 3.98 (1.74-8.21) with significant difference of p-0.01. The total leucocyte count before treatment was 6,725 (5,112-12,375) mm^3 while after treatment was 7,220 (6,990-9920) mm^3 with an insignificant difference of p-0.08. An Absolute Neutrophil Count (ANC) before treatment was 3,200 (1900-4500) mm^3 while after treatment was 4,850 (3120-6600) mm^3 with an insignificant difference of p-0.08. An Absolute Lymphocyte Count (ANC) before treatment was 3,980 (1850-6900) mm^3 while after treatment was 2,900 (1600-4200) mm^3 with an insignificant difference of p-0.053. Before treatment, Neutrophil to Lymphocyte Ratio was 7.2 (3.52-9.20) while after treatment was 3.34 (2.73-5.42) with a significant difference of p-.04. C - reactive protein (CRP) before treatment was 17.4 (6.25-53.40) while after treatment was 6.45 (3.20-29.50) with a significant difference of p-0.03. Erythrocyte Sedimentation Rate (ESR) before treatment was 38 (12-58) while after treatment was 22 (7-38) with a significant difference of 0.04. Lactate Dehydrogenase (LDH) before treatment was 244 (174.50-302.75) U/L while after treatment was 248 (184.6-310.50) U/L with an insignificant difference of p-0.08. Serum Albumin before treatment was 3.4 (3.15-4.20)g/dl while after treatment was 3.74 (3.24-4.80) g/dl with an insignificant difference of p-0.07.

Serum Uric Acid before treatment was 4.77 (3.54-6.28) while after treatment was 4.20 (2.99-5.90) with an insignificant difference of p-0.054 [Table 2].

Table No.I: Baseline demographics of patients included in the study (n=237)

Variable		Frequency (%) / Mean ± S.D.
Age (years)		52.47 ± 15.5
Tumor Size (cm)		3.54 ± 2.30
Gender	Male	90 (38 %)
	Female	147 (62 %)
Diagnosis	Lymphoma (Hodgkin + Non-Hodgkin)	72 (30.4 %)
	Gynecological Tumors	43 (18.1 %)
	Lung Cancer	36 (15.2 %)
	Gastrointestinal Tract Tumors	32 (13.5 %)
	Genitourinary Tumors	23 (9.7 %)
	Head and Neck Tumors	12 (5.1 %)
	CNS Tumors	09 (3.8 %)
	Colorectal Cancer	06 (2.5 %)
	Sarcoma	02 (0.84 %)
	Melanoma	02 (0.84 %)
Positive Lymph Nodes	0	114 (48.1 %)
	1-3	45 (19 %)
	4-9	36 (15.2 %)
	>10	24 (10.1 %)
	Not Known	18 (7.6 %)
Metastasis	Yes	93 (39.2 %)
	No	144 (60.8 %)
TNM Stage	1	19 (8 %)
	2	62 (26.3 %)
	3	53 (22.4 %)
Lympho vascular Invasion	Yes	130 (54.9 %)
	No/ Not Known	107 (45.1 %)

Table No.2: Cross-tabulation of SUV max and various hematological parameters before and after treatment (n=237)

Variables	Before Treatment	After Treatment	p-value
	Mean ± IQR		
SUV max	10.35 (5.8-12.84)	3.98 (1.74-8.21)	0.01
Total Leucocyte Count (mm^3)	6,725 (5,112-12,375)	7,220 (6,990-9920)	0.08
Absolute Neutrophil Count (mm^3)	3,200 (1900-4500)	4,850 (3120-6600)	0.08
Absolute Lymphocyte Count (mm^3)	3,980 (1850-6900)	2,900 (1600-4200)	0.053
Neutrophil to Lymphocyte Ratio	7.2 (3.52-9.20)	3.34 (2.73-5.42)	0.04
C-Reactive Protein (CRP)	17.4 (6.25-53.40)	6.45 (3.20-29.50)	0.03
Erythrocyte Sedimentation Rate (ESR)	38 (12-58)	22 (7-38)	0.04
Lactate Dehydrogenase (LDH) (U/L)	244 (174.50-302.75)	248 (184.6-310.50)	0.08
Serum Albumin (g/dl)	3.4 (3.15-4.20)	3.74 (3.24-4.80)	0.07
Serum Uric Acid	4.77 (3.54-6.28)	4.20 (2.99-5.90)	0.054

DISCUSSION

The results of our study reported that from the 237 patients included, a significant difference was observed in the pre and post treatment values of SUV max (p-0.01), NLR (p-0.04), C-reactive protein (p-0.03) and ESR (p-0.04). Majority of patients included were females (62 %) with the highest diagnosis being of lymphoma (30.4 %) followed by gynecological tumors (18.1 %), lung cancer (15.2 %) and gastrointestinal tumors (13.5 %) while least common diagnosis was of sarcoma and melanoma in 0.84 % of patients each.

In line with our study, other studies have reported similar results in terms of the SUV max uptake values of Positron Emission Tomography/ Computed Tomography before and after treatment as well as the values of NLR[16]. This study is one of the first study in which both PET/CT and NLR were evaluated in same set of patients. A study reported that PET/CT plays an important role in localization of lesion and can be used as a useful technique for directing course of initial therapy of in patients where biopsy is risky, such as with suspected recurrence or cancer near vital organs[17]. PET/CT is effective in distinguishing malignant from benign tumors as well[18]. Like in our study as well, another study observed that PET/CT can be successfully used for determining extent of cancer treatment especially in treatment that may require additional therapy.

Researchers have deemed it vital for predicting biological behavior, prognosis as well as patient followed in various cancers. There are multiple methods for such predictions, but it is not yet clear as to which modality is best[19]. Similar to PET/CT, the use of NLR as an inflammatory marker in tumorigenesis has been studied. Published data shows that a high NLR has been associated with poor prognosis while low NLR has been linked to better prognosis. However, it is stated that NLR might be an objective measure of

inflammation with can easily be derived from routine laboratory assessments[20]. A study done to evaluate the utility of NLR in cancer patients concluded that NLR is a validated independent prognostic factor for cancer patients after treatment[21].

Another research done by Ucar E et al for finding a relationship between laboratory parameters and SUV max of PET/CT in lymphoma patients observed that CRP, ESR and LDH values were good predictors of treatment in addition to PET/CT and also in patients where PET/CT imaging could not be performed. Similar results were reported in our study as well[21].

In yet another analysis of over 60 studies with 37,000 cancer patients, various studies were found to have elevated levels of NLR and were associated with poor prognosis. A study by on colorectal cancer patients observed mean NLR to be >4. Gastric cancer patients reported NLR >3. A research on pancreatic cancer patients observed NLR >5, on lung cancer patients NLR was >2.5, in renal cancer patients NLR was >2.5 etc. One common factor in all the studies was that in patients having decreased NLR after treatment showed better prognosis than in patients having a high NLR after treatment, being associated with poor prognosis.

The findings of our study are in line with the published literature. However one strength of the our study is that both PET/CT and NLR have not been evaluated. This was one of a kind study where both were evaluated. Nonetheless our study was not free from limitations such selection bias, technical errors, the fact that the study was carried out at a single center with limited sample size etc. Further multi-centered local studies would help in validating the findings of this study.

CONCLUSION

According to the results of the study, both SUV max uptake of PET/CT imaging showed significant decrease after treatment of cancer patients. Similarly NLR was also found to decrease after treatment. Both were associated with better prognosis of patients.

Author's Contribution:

Concept & Design of Study:	Reena Kumari Sunil
Drafting:	Tariq Siddique, Tooba Khan
Data Analysis:	Sunil Kumari
Revisiting Critically:	Reena Kumari Sunil
Final Approval of version:	Reena Kumari Sunil

Conflict of Interest: The study has no conflict of interest to declare by any author.

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