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Overall survival predictive significance of initial biological parameters and FDG-PET-CT parameters in patients with multiple myeloma.

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Abstract:
Aim of work: In the current study, we aimed to investigate the added prognostic value of initial 18F-FDG PET/CT in patients with multiple myeloma on overall survival.

Patients and Methods: This prospective study enrolled 50 adult patients with pathologically proven multiple myeloma, referred for initial pre-therapy and post-therapy FDG-PET-CT studies. Initial laboratory investigations were also done. Semi-quantitative analysis was done. Follow up period was 6 – 24 months.
Results: among the 50 patients; Patients with plasma cell count more than >10 %) (P value 0.026) and albumin to globulin ratio ≤0.5 showed significantly lower overall survival compared to other patients. Regarding initial PET-CT derived volumetric parameters; there was no statistical significance regarding prediction of overall survival.
Conclusion: Biological data (A/G ratio) could have a valuable predictive value for overall survival.
Keywords: 18F-FDG PET/CT, Volumetric Parameters, multiple myeloma.

Introduction:

Although multiple myeloma (MM) was considered as rare plasma cell neoplasm, it's currently classified as the second most common hematological malignancy, constituting 10-15% of all blood malignancy [1, 2]. Based on Global Cancer Observatory (GLOBOCAN) statistics, there were a global increase in its incidence by 126 % from 1990 to 2016. [3]. Death from MM compared to other neoplasms represents 1.1 %, whereas 74.8 % of patients shows 5-year survival[1].

Multiple myeloma characterized by abnormal monoclonal plasma cell proliferation in the bone marrow resulting in lytic changes that predominantly affects axial skeleton by 49% in vertebral bodies, 35% in cranial bones, 34% in pelvic bones, 33% in ribs and shafts of long bones [4].

Anaemia is a common presentation. One fifth of patients will show signs of renal impairment and it can get severe in less than 5%. Most patients usually present with bony aches, pathological fracture and some patients show hypercalcemia. These manifestations are referred as **CRAB criteria**[5,6].

The international stating system (ISS); a three-stage scoring system implemented as a biological biomarker for detection of overall survival in MM. serum albumin and B 2 microglobulin are the main tools used by ISS. The revised-ISS (RISS) added LDH and cytogenetics. According to the RISS; Patients with stage I show favorable overall survival, while patients with stage III show poor survival [7, 8].

The aim of the current study is detection of overall survival predictive value of initial laboratory data compared to FDG-PET-CT in patients with multiple myeloma.

Patients and methods:

Population of study & disease condition:

- This prospective study enrolled 60 adult patients pathologically proven as plasma cell myeloma. They were all referred to Nuclear Medicine unit for initial pre-therapy assessment in the National Cancer Institute (NCI), between the periods of March 2021 to November 2023.

Inclusion criteria:

- Patients with pathologically proven plasma cell myeloma.
- Referred for initial assessment.
- No prior surgical, chemo or radiotherapy.

Exclusion criteria:

- Patients with double primary, pregnancy, uncontrolled DM.
- Patients who are not fulfilling any of the fore- mentioned criteria.

Clinical diagnosis:

- All patients underwent clinical examination assessing vitals, range of movement, sites of severe pain or fractures if present.
- Detailed clinical and family history was acquired.
- Initial laboratory tests done including (Hemoglobin level, urea, creatinine, serum free and ionized calcium, LDH, B2M)
- Serum electrophoresis blood test is done to detect total proteins, albumin, globulin and A/G ratio.
- Serum immunofixation test is done to classify the abnormal M protein detected.
- Patients were classified according to the revised international staging system into **either stage I** (Serum albumin ≥ 35 g/L, Serum β2-microglobulin <3.5 mg/L, Normal serum LDH), or **stage III** (β2-microglobulin >5.5 mg/L or elevated serum LDH) or **stage II** (that's neither I or III).

Initial and post-therapy Plasma cell percentage from BMB / BMA:

- Bone marrow aspiration (BMA) followed bone marrow biopsy (BMB) were done for each patient at initial presentation and by the end of treatment after 24 weeks. Plasma cell percentage was determined. CD138 percentage by immunohistochemistry was furtherly evaluated by BMB.

18-F-FDG-PET-CT:

All patients were referred for initial and end of treatment PET-CT studies. Preparation for PET-CT included:

- Fasting for 6 hours before the study.
- Low carbohydrates diet the day before the exam.
- Blood glucose level less than 160 mg/dl.
- No prior strenuous exercise of heavy physical activity.

The study was interrupted by two different experienced physicians on a specific workstation. Metabolic parameters were extracted for each patient and correlated with overall survival.

Evaluation of clinical response and survival:

Personnel clinical follow up data and BMB were collected for each individual patient to establish the patient's clinical response (according to PERCIST criteria) as follow:

- **Complete response**; Negative PET-CT in addition to negative BMB.
- **Partial response;** stationary or decrease more than 30% in SUV on PET/CT.
- **Progressive disease**; progression of the old detected lytic lesions or newly developed lesions with progression in plasma cell counts.
- **Stable disease;** decrease less than 30% in SUV of initial osseous lesions with no appearance of new lesions in PET/CT or CT.

Statistical methods:

Data management and analysis were performed using Statistical Package for Social Sciences (SPSS) vs. 27. Comparisons between two groups for normally distributed numeric variables were done using the Student's t-test while for non-normally distributed numeric variables, comparisons were done by Mann-Whitney test.

The overall survival was estimated using the Kaplan and Meier method. Overall survival was calculated from date of diagnosis to date of death or last follow up. Differences between the survival curves were assessed with the log-rank test. All tests were two tailed & Probability (p-value) ≤ 0.05 is considered significant.

Results:

The current study included 50 adult patients pathologically proven with multiple myeloma enrolled from Nuclear Medicine and Medical Oncology department at National Cancer Institute, Cairo University. Patients were referred for initial staging by FDG PET/CT and after 24 weeks at end of treatment PET-CT with median follow up duration 18 months ranging from 2 to 35 month. The average age of the patients was 57 years old ±10 with male to female ratio was 1.3:1.

Clinico-laboratory characteristics of patients with multiple myeloma:

Most of the patients presented with anemia with mean hemoglobin level at initial presentation of 9.8 mg/dL. Mean creatinine level was 1.5 mg/dL. The mean calcium level was at normal range of 9.2 mg/dL, mean LDH 283.9 U/L and B2M was 5 mcg/ml. by bone marrow biopsy; the median plasma cell count was 20 ranging from (0.2-80). By protein electrophoresis, 33 patients presented with elevated total proteins with mean level of 9.2 9/dl. 31 patients presented with elevated globulin levels with mean level of 5.3 g/dl. 40 patients presented with decreased A/G ratio with mean ratio of 0.6 %. Laboratory data of the patients were shown in **table (1).**

Table (1): Laboratory data of 50 patients with multiple myeloma:

	Mean ± SD
HB	9.8 ±1.7
Calcium	9.2 ±1
LDH	283.9 ±124.1
T. proteins	9.2 ±2.1
Plasma cells	26.4 ±18.8
Globulin	5.3 ±2
	Median (range)
Creatinine	1.5 (0.6-8.8)
B2m	5 (1.6-17.2)
A/G	0.6 (0.2-1.9)

Correlation of laboratory data in multiple myeloma patients with overall survival:

There was no statistically significant difference in overall survival in relation to age, sex, serum calcium level, creatinine, B2m, LDH, total protein. No statistically significant FDG PET-CT volumetric parameter could be correlated to overall survival.

By protein electrophoresis, 33 patients presented with elevated total proteins with mean level of 9.2 9/dl. 31 patients presented with elevated globulin levels with mean level of 5.3 g/dl. 40 patients presented with decreased A/G ratio with mean ratio of 0.6 %.

Regarding A/G ratio, patients with A/G ratio ≤0.5 had significantly lower overall survival compared to patients with A/G ratio >0.5 (P value 0.001). Patients with A/G ratio ≤0.5 had eight times more risk of mortality compared to patients with A/G ratio >0.5. (Table 2, figure 1).

Table (2): Overall survival in relation to demographic and laboratory data in patients with MM:

	No of cases	Survival % at 1 year	Survival % at 2 years	P value
Whole group	50	74	74	
Age				0.806
Calcium				0.930
Creatinine				0.209
B2m				0.267
LDH				0.394
A/G				
≤0.5	23	52	52	**0.001**
>0.5	27	93	93	

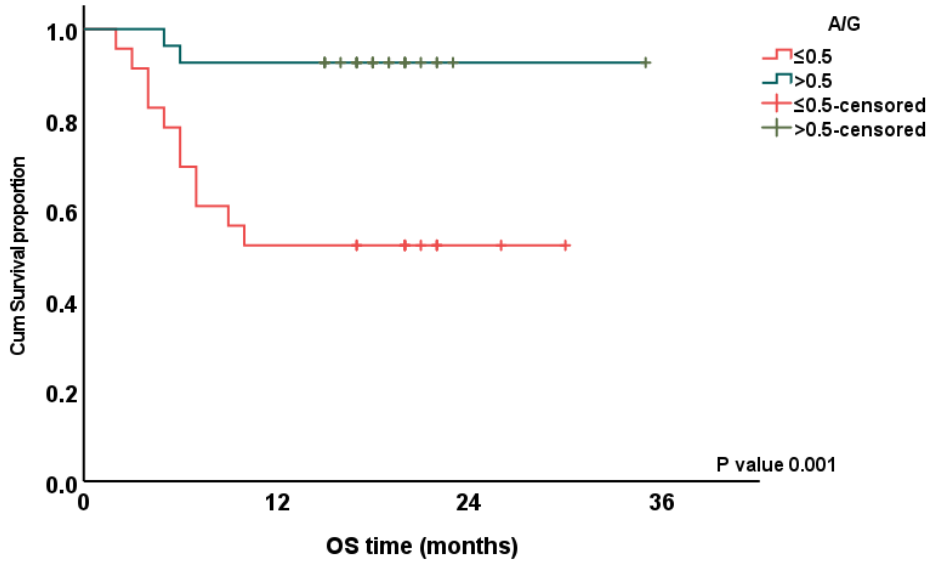

Figure (1): Relation of A/G to overall survival of 18 months

Correlation of FDG PET/CT derived metabolic parameters in multiple myeloma patients with overall survival:

Regarding initial PET-CT derived metabolic parameters; a cut off value was done for every parameter, yet there was no statistically significant difference in overall survival in relation to initial PET CT volumetric parameters (table 3).

Table (3): Overall survival in relation to initial PET-CT volumetric parameters in patients with MM:

	Survival % at 1 year	Survival % at 2 year	P value
SUV max			
≤7	85	85	0.078
>7	63	63	
SUV mean			
<3	85	85	0.078
≥3	63	63	
SUV peak			
≤5	82	82	0.274
>5	68	68	
MTV			
<50	67	67	0.189
≥50	83	83	
TLG			
<350	74	74	0.987
≥350	73	73	

Discussion:

Multiple myeloma is a heterogenous hematological neoplastic disease characterized by abnormal plasma cell infiltration of the bone marrow. It's a multi-step disorder evolving from asymptomatic precursors (MGUS / SMM), till the inevitable presentation of lytic osseous lesions. Early diagnosis, adequate initial staging and monitoring during course of treatment can prevent progression or relapse after bone marrow transplantation.

In the current study, we investigated the added value of initial and interim (after 12 weeks of treatment) PET-CT volumetric parameters as a prognostic tool in patients with multiple myeloma for the detection of treatment response and/or overall survival. We included in the study 60 patients, histo-pathologically proven multiple myeloma, underwent initial, interim and post-therapy PET-CT. Volumetric parameters solely and in combined with initial laboratory data were correlated for the detection of overall outcome.

In the current study, by protein electrophoresis, most patients presented with elevated total proteins, elevated globulin levels and decreased A/G ratio with mean levels of (9.2 g/dl, 5.3 g/dl and 0.6 %) respectively.

For **prediction of overall survival**, as regards laboratory data; Patients **with A/G ratio ≤0.5** (P value 0.001) show poor overall survival. It was noted that Patients with A/G ratio ≤0.5 had eight

times more risk of mortality compared to patients with A/G ratio >0.5. There was no statistically significant difference in overall survival in relation to (age, sex, calcium, creatinine, B2m, LDH and toral protein).

Also, **Cai et al** in patients with multiple myeloma with median follow-up period was 36 months. The optimal cutoff of A/G ratio was 1.16 according to receiver operating characteristic curve analysis. High AGR was significantly correlated with better overall survival (OS)[9].

On the contrary, a study done by **Hussain et al;** Elevated LDH, advanced age >70 years ($p<0.001$), Hb <10 g/dl ($p<0.001$) and renal impairment ($p=0.001$) were all associated with overall poor outcome [10]. **GU et** al; correlated LDH levels with overall survival and disease progression, where higher LDH levels were associated with increased risk of death ($p = 0.003$) and increase risk of disease progression ($p = 0.035$) [11]. And another study done by **McDonald et al**; patients with initial PET/CT; initial TLG exceeding 620g and primary MTV exceeding 210 cm^3 were statistically significant associated with OS [12].

Conclusion:

PET-CT derived volumetric parameters showed no significant value in the detection of overall survival, however biological data (A/G ratio) could have a valuable predictive value for overall survival.

References:

1.	Padala SA, Barsouk A, Barsouk A, et al. Epidemiology, Staging, and Management of Multiple Myeloma. Med Sci (Basel). 2021. doi:10.3390/medsci9010003.2021.
2.	Charliński G, Jurczyszyn A. Non-secretory multiple myeloma: Diagnosis and management. Adv Clin Exp Med. 2022;31(1):95-100. doi:10.17219/acem/141455,2022.
3	Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries [published correction appears in CA Cancer J Clin. 2020 Jul;70(4):313]. CA Cancer J Clin. 2018;68(6):394-424. doi:10.3322/caac.21492,2018.
4	Silbermann R, Roodman GD. Myeloma bone disease: pathophysiology and management. Journal of bone oncology. 2013;2(2):59-69, 2013.
5	Mughal TI, Goldman JM and Mughal ST. understanding leukemias, lymphomas and myelomas book. 2007.

6	Cowan AJ, Green DJ, Kwok M, et al. Diagnosis and Management of Multiple Myeloma: A Review. JAMA. 327(5):464-477. 2022, doi:10.1001/jama.2022.0003, 2022.
7	Durie BG, Salmon SE. A clinical staging system for multiple myeloma. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. Cancer. 36(3):842-854. 1975, doi:10.1002/1097-0142(197509)36:3<842::aid-cncr2820360303>3.0.co;2-u, 1975.
8	Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised International Staging System for Multiple Myeloma: A Report From International Myeloma Working Group. J Clin Oncol. 2015; doi:10.1200/JCO.2015.61.2267. 2015.
9	Cai Y, Zhao Y, Dai Q, et al. Prognostic value of the albumin-globulin ratio and albumin-globulin score in patients with multiple myeloma. J Int Med Res. 49(3):300060521997736. 2021, doi: 10.1177/0300060521997736. PMID: 33682516; PMCID: PMC7944530, 2021.
10	Nanni C. PET-FDG: Impetus. Cancers (Basel). 2020;12(4):1030. Apr 22. 2020, doi:10.3390/cancers12041030. 2020.
11	Gu Y., Yuan Y., Xu J., et al. High serum lactate dehydrogenase predicts an unfavorable outcome in Chinese elderly patients with multiple myeloma. Oncotarget. 8: 48350-48361. 2017; doi.org/10.18632/oncotarget.16237, 2017.
12	McDonald JE, Kessler MM, Gardner MW, et al. Assessment of Total Lesion Glycolysis by 18F FDG PET/CT Significantly Improves Prognostic Value of GEP and ISS in Myeloma. Clin Cancer Res. 23(8):1981-1987. 2017; doi:10.1158/1078-0432.CCR-16-0235, 2017.