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Comparison between circulating biomarkers Serum CRP and Plasma Fibrinogen levels In Malignant Pleural Mesothelioma patients Before and After Surgical and Chemotherapy Modalities

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Abstract: In our study we are measured a novel blood biomarkers as Serum CRP, And Plasma Fibrinogen levels of MPM patients, initially and after one month of treatment even surgical or chemo radiotherapy in multimodality therapy. In our study we are found that Plasma Fibrinogen is a significant biomarker of MPM to determine the prognosis of MPM patients, and determine the efficacy and the achieved benefits of surgical treatment for that patients. And Plasma fibrinogen levels are most sensitive and significant than Serum CRP of prognosis of MPM and determine the achieved benefits from surgery within multimodality therapy. Surgery within multimodality therapy of MPM, increase the survival rate of the MPM pts more than chemo radiotherapy of that pts.

Keywords: Comparison; circulating; biomarker; Serum; CRP; Plasma; Fibrinogen; Malignant; Pleural; Mesothelioma; patient; Surgical; Chemotherapy; Modality

1. Introduction

Mesothelioma is considered one of the most serious and lethal cancers worldwide, Increasing of Incidence and prevalence rate of MPM is strongly related to asbestos exposure and chronic inflammation. And expected that the incidence rate continues to rise, reaching the peak by 2020.

Especially at regions and countries which are fulfilled with asbestos related factories and materials, Screening programs for early detection of MPM, protective safety protocols of asbestos exposure should be considered.

In spite of presence of varieties of treatment modalities of MPM which included surgical modalities, chemotherapy, and radiation modalities, there is no definitive cure of MPM until now.

The aim and goals of all treatment modalities are challenging, increasing the life expectancy, increasing the overall survival rate, and improving the quality of life for the diseased pts.

And therefore, several studies and researches on biomarkers are carried out, which are considered the predictors and prognostic factors for MPM.

Regarding MPM is strongly related to chronic inflammation,

Serum c-reactive protein (crp) and plasma fibrinogen levels at time of diagnosis are considered one of the most important prognostic and predictive biomarkers for mpm, they can predict the prognosis and the response to treatment modalities.

In our study, prospective cohort study, we measured serum CRP and Plasma Fibrinogen level of MPM at time of diagnosis and one month post treatment to evaluate the achieved benefits and outcomes of treatment modalities and their effects on prognosis.

2. Patients and Methods

This study is an epidemiological observational prospective cohort study aimed to compare between measurements of circulating biomarkers serum CRP, And plasma Fibrinogen levels in MPM patients undergoing surgical within multimodality therapy or chemo-radiotherapy and follow up the same biomarkers after one month from the planned therapy, and to evaluate the achieved overall survival and outcome of the therapeutic modalities.

This study was conducted at the Department of cardiothoracic surgery in Ain Shams hospital, Ain Shams university, Departments of Medical oncology and Cardiothoracic surgery in Kasr Alaini Hospital, Cairo university, Departments of Medical oncology and oncosurgery in National Cancer Institute (NCI).

It was carried out within 9 months duration, from December 2018to August 2019.

Patient population:

The study includes,60 patients of MPM, diagnosed and proven by pleural tissue biopsy, By staging of the disease according TNM staging, and by clinical and investigation assessment, Group A (n =30) were good performance status (PS 0-2), and fit for surgery. they underwent surgery within multimodality. Group B (n=30) were not good performance status (3-4), unfit for surgery, and some refused surgery, received chemo-radio therapy.

After approval of the local ethical committee and obtaining an informed verbal consent from every patient, patients were selected according to the following inclusion and exclusion criteria.

Inclusion Criteria:
Patients initially diagnosed with MPM who will undergo either surgery, chemo-radiotherapy therapeutic modalities according to disease stage, and clinical and investigation assessment according to guidelines.

Exclusion criteria:
1. Hemodynamically unstable patients.
2. Patients with coagulopathy disorders.
3. Patients with acute infection before surgery or any intervention.
4. Any contraindication for surgery as distant metastases.
5. Patients already who already under one of the therapeutic modalities either chemo or radiotherapy.

Statistical analysis:
Data were analyzed using Statistical Program for Social Science (SPSS) version 15.0. Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

The following tests were done:
Independent-samples t-test of significance: was used when comparing between two means.
Chi-square test: was used when comparing between non-parametric data.

Probability (P-value)
– P-value <0.05 was considered significant.
– P-value <0.001 was considered as highly significant.
– P-value > 0.05 was considered insignificant.

3. Results
Table (1) shows the description of demographic data of studied patients.

As regard age, the mean of age in studied patients was 58.9± 5.8years with minimum age of 48 years and maximum age of 68years.

As regard sex, there were 44 males (73.3%) and 16 females (26.7%) in the studied patients.

As regard weight, the mean of weight in studied patients was 71.9± 11.5kg with minimum weight of 55 kg and maximum weight of 95kg.

As regard height, the mean of height in studied patients was 1.69± 0.05m with minimum height of 1.61 m and maximum height of 1.78m.

As regard BMI, the mean of BMI in studied patients was 25.5± 4.2kg/m^{2}with minimum BMI of 20.3 kg/m^{2}and maximum BMI of 37.1 kg/m^2.

As regard special habit, there were 37 non-smoker (61.7%) and 23 smoker (38.3%) in the studied patients.

Table (1): Description of demographic data of studied patients.

Variables		Studied patients (N = 60)	
Age (years)	Mean ±SD	58.9 ± 5.8	
	Min - Max	48 - 68	
Sex (n, %)	Male	44	73.3%
	Female	16	26.7%
Weight (kg)	Mean ±SD	71.9 ± 11.5	
	Min - Max	55 - 95	
Height (m)	Mean ±SD	1.69 ± 0.05	
	Min - Max	1.61 - 1.78	
BMI (kg/m^2)	Mean ±SD	25.5 ± 4.2	
	Min - Max	20.3 - 37.1	
Special habit (n, %)	Non	37	61.7%
	Smoker	23	38.3%

Table (2): Description of performance status and type of treatment of studied patients.

Variables		Studied patients (N = 60)	
Performance status	PS (0-2)FIT	30	50%
	PS (3-4)UNFIT	30	50%
Type of treatment	Surgical	30	50%
	Chemotherapy	30	50%

This table shows Description of performance status and type of treatment of studied patients. **As regard performance status,** there were 30patients (50%) PS (0-2) FIT and 30patients (50%) PS (3-4) UNFIT in the studied patients. **As regard type of treatment,** there were 30patients (50%) had surgical treatment and 30patients (50%) had chemotherapy in the studied patients.

Table (3): Description of surgical procedure done in surgical group.

		Surgical group (N = 30)	
Surgical procedure	Extra Pleural Pneumonectomy	3	10%
	Pleurectomy/Decortication	20	66.7%
	Palliative Debulking Pleurectomy	7	23.3%

This table shows Description of surgical procedure done in surgical group. There were 3 patients (10%) subjected to extra plural pneumonectomy, 20 patients (66.7%) subjected to plurectomy/decortication and 7 patients subjected to palliative debulking pleurectomy.

Table (4): comparison between studied groups as regard CRP and Fibrinogen.

Variables		Surgical (N = 30)	Chemotherapy (N = 30)	P-value
CRP (before)	Mean	85.03	105.37	< 0.001
	±SD	14.51	12.04	HS
CRP (After)	Mean	30.63	36.67	0.097
	±SD	13.94	13.72	NS
Fibrinogen (before)	Mean	762.00	833.93	< 0.001
	±SD	47.27	49.28	HS
Fibrinogen (After)	Mean	228.90	335.20	< 0.001
	±SD	60.02	35.17	HS

HS: p-value < 0.001 is considered highly significant. NS: p-value > 0.05 is considered non-significant.

This table shows:
- No statistical significant difference **(p-value > 0.05)** between surgical and chemotherapy groups as regard CRP after one month of treatment.
- Highly statistical significant difference **(p-value < 0.001)** between surgical and chemotherapy groups as regard CRP before treatment.
- Highly statistical significant difference **(p-value < 0.001)** between surgical and chemotherapy groups as regard fibrinogen before treatment.
- Highly statistical significant difference **(p-value < 0.001)** between surgical and chemotherapy groups as regard fibrinogen after one month of treatment.

Table (5): comparison between CRP and Fibrinogen before and after therapy in surgical group.

Surgical Variables		Before (N = 30)	After (N = 30)	% of reduction	P-value
CRP	Mean	85.03	30.63	64%	< 0.001
	±SD	14.51	13.94		HS
Fibrinogen	Mean	762.0	228.9	70%	< 0.001
	±SD	47.27	60.02		HS

HS: p-value < 0.001 is considered highly significant.

This table shows highly statistical significant difference **(p-value < 0.001)** between CRP and Fibrinogen before and after therapy in surgical group.

Table (6): comparison between CRP and Fibrinogen before and after therapy in chemotherapy group.

chemotherapy Variables		Before (N = 30)	After (N = 30)	% of reduction	P-value
CRP	Mean	105.37	36.67	65.2%	< 0.001 HS
	±SD	12.04	13.72		
Fibrinogen	Mean	833.93	335.20	59.5%	< 0.001 HS
	±SD	49.28	35.17		

HS: p-value < 0.001 is considered highly significant.

This table shows highly statistical significant difference **(p-value < 0.001)** between CRP and Fibrinogen before and after therapy in chemotherapy group.

Table (7): comparison between studied groups as regard overall survival rate 8 months.

Variables		Surgical (N = 30)		Chemotherapy (N = 30)		P-value
Overall survival rate	Survived	30	100%	26	86.7%	0.038 S
	Died	0	0%	4	13.3%	

S: p-value < 0.05 is considered significant.

This table shows statistically significant difference **(p-value < 0.05)** between studied groups as regard overall survival rate 8 months.

Table (8): Description of neo adjuvant chemo drugs of surgical group.

Variables		Surgical group (N = 30)	
neo adjuvant chemo drugs	Alimta	10	33.3%
	Alimta+Cisplatin	20	66.7%

This table shows neo adjuvant chemo drugs in surgical group. There were 10 patients (33.3%) received ALIMTA and 20 patients (66.7%) received ALIMTA + CISPLATIN.

Table (9): comparison between of CRP and Fibrinogen as regard neo adjuvant chemo drugs in surgical group.

Surgical Variables		Alimta (N = 10)	Alimta+Cisplatin (N = 20)	P-Value
CRP (before)	Mean	75.20	89.95	0.006 S
	±SD	11.67	13.43	
CRP (After)	Mean	23.80	34.05	0.056 NS
	±SD	13.97	12.93	
Fibrinogen (before)	Mean	723.90	781.05	0.001 S
	±SD	43.23	37.13	
Fibrinogen (After)	Mean	195.60	245.55	0.012 S
	±SD	38.42	62.65	

S: p-value <0.05 is considered significant. NS: p-value > 0.05 is considered non-significant.

This table shows:
- Statistically significant difference **(p-value < 0.05)** between ALIMTA group and ALIMTA + CISPLASTIN group of surgically treated patients as regard CRP (before) and Fibrinogen (before and after).

- No statistically significant difference **(p-value > 0.05)** between ALIMTA group and ALIMTA + CISPLASTIN group of surgically treated patients as regard CRP (after).

Table (10): Description of palliative chemotherapy drugs of chemotherapy group.

Variables		Chemotherapy group (N = 30)	
Palliative chemotherapy drugs	ALIMTA	7	23.3%
	ALIMTA+CISPLATIN	23	76.7%

This table shows palliative chemotherapy drugs in chemotherapy group. There were 7 patients (23.3%) received ALIMTA and 23 patients (76.7%) received ALIMTA + CISPLATIN.

Table (11): comparison between of CRP and Fibrinogen as regard palliative chemotherapy drugs in chemotherapy group.

Chemotherapy Variables		ALIMTA (N = 7)	ALIMTA +CISPLATIN (N = 23)	P-value
CRP (before)	Mean	93.43	109.0	0.001
	±SD	2.64	11.41	S
CRP (After)	Mean	29.57	38.83	0.022
	±SD	5.8	14.77	S
Fibrinogen (before)	Mean	780.14	850.30	< 0.001
	±SD	17.91	43.74	HS
Fibrinogen (After)	Mean	316.14	341.0	0.019
	±SD	16.13	37.54	S

S: p-value < 0.05 is considered significant. HS: p-value < 0.001 is considered highly significant.

This table shows:
- Statistically significant difference **(p-value < 0.05)** between ALIMTA group and ALIMTA + CISPLASTIN group of chemotherapy treated patients as regard CRP (before and after) and Fibrinogen (after).
- Highly statistically significant difference **(p-value < 0.001)** between ALIMTA group and ALIMTA + CISPLASTIN group of chemotherapy treated patients as regard Fibrinogen (before).

4. Discussion

Regarding this results and by comparing them with other literatures, showing that:

Ghanim et al. (2014) reported, Among 176 pts whom were diagnosed and proven with MPM underwent surgery, retrospective study was performed and pretreatment serum CRP and plasma Fibrinogen levels were measured, the study reported that, most pts had elevated plasma fibrinogen level (>390mg/dl) and pts with low level of fibrinogen (<627mg/dl) had significantly longer overall survival (19.1 months), when compared with those high level (>627mg/dl) had short survival rate (8.5months), and proven that fibrinogen is anovel independent prognostic biomarker and predicted treatment benefit achieved by surgery within multimodality therapy, Although serum CRP at time of MPM diagnosis predict survival benefit achieved by macroscopic radical surgery within multimodality treatment, Patients with low Serum C-Reactive protein levels (CRP) at time of diagnosis had a significantly better prognosis with multimodality therapy including surgery when compared with patients with elevated serum CRP levels undergoing surgery with multimodality therapy.

Winter et al. (2012) reported, Among 115 pts whom were diagnosed with MPM, and underwent surgery, retrospective study was performed to evaluate the prognostic and predictive relevance of pretreatment serum CRP, and plasma Fibrinogen levels, Pts with elevated CRP levels had a significantly shorter overall survival compared with those with low CRP levels, and no survival benefit was achieved by radical surgery within multimodality approaches. Elevated Serum CRP levels was confirmed as an independent prognostic factor in MPM.

Hamid et al. (2019), Among 313 pts who underwent surgery for non-small – lung cancer (NSCLC), And preoperative blood results including plasma fibrinogen, c- reactive protein (CRP), hemoglobin concentration, And platelet count were included in the analysis. Reported, elevated preoperative plasma fibrinogen was an independent marker of reduced survival in pts with resected non-small- lung cancer, and it's value in selecting pts who may benefit from surgery, and pts with abnormal CRP,

Fibrinogen levels, and hemoglobin levels had a worse overall survival.

Zeng et al. (2017), Among 856 pts who underwent surgery for Non – small –cell lung cancer (NSCLC), Retrospectively preoperative evaluated of independent factors for survival were CRP, Fibrinogen, tumor status, nodal status, distant metastasis, and clinical stage.

On multivariate analysis of 856 cohort, established and reported a nomogram containing CRP, Fibrinogen for predicting survival of pts with resected NSCLC, and it shows superior discrimination ability compared with traditional TNM staging. Comparing with pts with low CRP and low Fibrinogen levels had longer overall survival than, pts with high CRP and high Fibrinogen levels had shorter overall survival, So, A nomogram integrating CRP and Fibrinogen, may assist in risk stratification for individual pts with resected NSCLC.

Sheng et al (2013), Among 684 pts underwent surgery for NSCLC, Fibrinogen concentration was analyzed to evaluate the association between the clinic pathological variables and serum fibrinogen levels, respectively. the correlation between fibrinogen and CRP was determined through the analysis, and reported that, serum fibrinogen preoperative was an independent prognostic factor in operable NSCLC patients pts with hyperfibrinogenemia had 1.49 times the risk of disease progression and 1.64 times the risk of death of those with low fibrinogen levels Fibrinogen Concentrations was significantly associated with clinical tumor stage and pts outcome. Elevated serum fibrinogen concentrations was associated with worse patients outcomes. Plasma fibrinogen is a new independent prognostic biomarker for progression – free and overall survival in operable NSCLC pts, and should be assessed in the workup of pts with NSCLC, Serum CRP concentrations was not correlated with progression - free and overall survival.

Zhong et al (2018), Among 168 pts who underwent surgery for NSCLC, meta-analysis was done to assess the prognostic value of plasma fibrinogen in lung cancer, and the results of " cut off value ≥ 400 mg / dl " showed that the high level of fibrinogen in serum was associated with worse overall survival, and reported that Elevated plasma fibrinogen concentration of ≥ 400 mg / dl could be a promising indicator for worse overall survival in lung cancer patients, including NSCLC.

Jones et al (2006), Among 93 pts who underwent surgery for Non-Small Cell lung Cancer (NSCLC), Preoperative Plasma fibrinogen concentration and Serum CRP concentration were assessed to determine their association with tumor characteristics and to ascertain any role in patient selection for curative resection, The parameters were compared with tumor size, TNM stage, and possibility of complete resection in pts with NSCLC, Reported Plasma fibrinogen and serum CRP are associated with tumor characteristics. High values were associated with inability to achieve complete resection which may refine patient selection for thoracotomy when used with other staging modalities.

Gan, et al (2018), Among 768 patients with HCC hepatocellular carcinoma, who underwent effective prognostic indexes, (FC-SCORE) which incorporates fibrinogen and c- reactive protein CRP, was established. and reported that, (FC –SCORE) represents a novel, convenient, reliable, and accurate prognostic predictor for (OS) overall survival in patients with HCC undergoing curative resection.

Tian, et al (2016), Among 260 patients with histopathologically diagnosed esophageal squamous cell carcinoma (ESCC), 185 of those pts underwent curative transthoracic esophagectomysurgery, preoperative plasma Fibrinogen, serum CRP A, and albumin levels, postoperative survival were retrospectively reviewed and collected, classification of Pts according (FC SCORE) to FC SCORE 0 / FC SCORE 1 OR 2, and, PTS with elevated fibrinogen (>4.0 G/DL) and CRP (≥10.0) levels were assigned an FC SCORE Of 2, those with only one of these two abnormalities were allocated A SCORE 1, and those with neither of the two abnormalities were assigned A SCORE OF 0, And classified according Modified Glasgow Prognostic SCORE (mGPS), PTS with decreased CRP (<10.0mg/dl) levels were allocated an mGPS SCORE of 0, PTS with both elevated CRP (>10 mg/dl) and Albumin (>35.0 g/l) were assigned a SCORE of 1, while PTS with both elevated CRP and decreased albumin (<35.0 g/l) were allocated a SCORE OF 2, REPORTED, Cumulative SCORE based on preoperative Plasma Fibrinogen and Serum CRP could predict long – term survival for esophageal squamous cell carcinoma.

Katsurahara, et al (2018), performed a retrospective cohort study including 187 Pts who underwent esophagectomy for esophageal squamous cell carcinoma (ESCC), examined postoperative CRP in esophageal cancer, and the relationship between postoperative CRP values according to the postoperative period and prognosis in esophageal cancer.

Reported, CRP levels is an independent prognostic factor for ESCC.

Kijima et al (2017), Among 99 pts with advanced esophageal squamous cell carcinoma, the study was to investigate the pretreatment plasma fibrinogen and neutrophil – lymphocyte ratio (NLR) in patients with advanced esophageal squamous cell carcinoma, pts with advanced esophageal cell carcinoma (ESCC) are received chemo radiotherapy or

chemotherapy, combined SCORE using these blood markers named as the F-NLR (Fibrinogen and NLR) SCORE, as a predictor of tumor response and prognosis, F-NLR score of 2, having both hyperfibrinogenemia (>400 mg/dl) and high NLR (>3.0), score of 1, one of these hematological abnormalities, and score of 0, having neither hyperfibrinogenemia nor high NLR. overall survival was significantly lower and shorter in pts with an F-NLR score of 2 than in those with an F-NLR score 0 or 1, By analysis reported, the F-NLR was one of the independent prognostic factors and F-NLR score is promising as a predictive marker for therapeutic effects and prognosis in pts with advanced ESCC.

Perisanidis et al (2015), Meta- analysis was done to examine the prognostic effect of circulating fibrinogen in solid tumors, data from 52 studies and 15,371 pts were summarized, An elevated baseline plasma fibrinogen was significantly associated with worse overall survival, The highest negative effect of elevated plasma fibrinogen on OS (overall survival) was demonstrated in Renal cell Carcinoma, followed by Head and Neck Cancer, And Colorectal Cancer, An elevated pretreatment plasma fibrinogen significantly correlates with decreased survival in pts with solid tumors.

Polterauer, et al (2009), Among 422 pts diagnosed and proven Epithelial Ovarian Cancer (EOC), pre-operative plasma Fibrinogen, and CRP levels were evaluated and correlated with clinic pathological parameters and pts survival, reported that, elevated plasma fibrinogen levels were associated with advanced tumor stage, and CRP levels were associated with disease-free and overall survival.

Preoperative plasma fibrinogen levels can be used as an independent prognostic parameter in pts with epithelial ovarian cancer (EOC).

Ghezzi et al (2010), among 336 women with endometrial cancer who underwent surgical resection, cohort study was done to investigate the prognostic significance of preoperative plasma fibrinogen concentrations, reported, plasma fibrinogen level may be of value in the prediction of outcome, improve the stratification of endometrial cancer patient at diagnosis.

De Martin, et al (2013), Among 403 patients with localized Renal Cell Carcinoma (RCC), preoperative serum CRP levels were evaluated to validate CRP levels as an independent marker for disease free survival in clinically localized renal cell carcinoma, and reported that, preoperative Hs- CRP levels may be included in standard prognostic modeling after surgery and may guide surveillance and inclusion in adjuvant clinical trials.

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